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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS

ROYAL SOCIETY OF MEDICINE
20 MAR
1911

TWENTY-FIFTH SESSION

HELD AT WASHINGTON, D. C.

MAY 3, 4, AND 5, 1910

VOLUME XXV

PHILADELPHIA
PRINTED FOR THE ASSOCIATION
1910

NOTICE.

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

DORNAN, PRINTER
701–709 ARCH STREET
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OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME.

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1886.	Francis Delafield.	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	Geo. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard.	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.

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1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
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1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.

ELECTED

1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Fischel, W. E., 2647 Washington Ave., St. Louis.
*1886. Fitz, Reginald H., 18 Arlington St., Boston.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
*1886. Forchheimer, F., 160 West 9th St., Cincinnati, Ohio.
1908. Freeman, R. G., 205 West 57th St., New York.
1894. Fussell, M. Howard, 189 Green Lane, Manayunk, Philadelphia.
1903. Futcher, Thomas B., 3 West Franklin St., Baltimore.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
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1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1898. Herrick, James B., 200 Ashland Boulevard, Chicago.
1898. Herter, C. A., 819 Madison Ave., New York.
1910. Hewlett, Albion W., 902 Baldwin Ave., Ann Arbor, Mich.
1900. Holt, L. E., 14 West 55th St., New York.
*1886. Hun, Henry, 149 Washington Ave., Albany, N. Y.
1907. Hunt, Reid, Hygienic Laboratory, cor. 25th and E Sts. N. W., Washington, D. C.
1901. Jackson, Henry, 380 Marlborough St., Boston.
*1886. Jacobi, A., 19 East 47th St., New York.
1899. James, Walter B., 17 West 54th St., New York.
*1886. Janeway, E. G., 36 West 40th St., New York.
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*1886. Kinnicutt, Francis P., 39 East 35th St., New York.
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1900. Koplik, Henry, 692 Madison Ave., New York.
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*1886. Longstreth, Morris, 1416 Spruce St., Philadelphia.
1910. Lord, Frederick T., 305 Beacon St., Boston.
1905. Macallum, A. B., University of Toronto, Toronto, Canada.
1902. MacCallum, M. G., Johns Hopkins Hospital, Baltimore.
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1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
1898. Mallory, F. B., Department of Pathology, Harvard Medical School, Boston.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolf, Medical School, Johns Hopkins University, Baltimore.
1905. Miller, Joseph L., 100 State St., Chicago.
1898. Mitchell, John K., 1730 Spruce St., Philadelphia.
*1886. Mitchell, S. Weir, 1524 Walnut St., Philadelphia.
1908. Moffitt, Herbert C., 1316 Sutter St., San Francisco, Cal.
1901. Morse, John Lovett, 70 Bay State Road, Boston.
1887. Musser, John H., 1927 Chestnut St., Philadelphia.
1891. Northrup, W. P., 57 East 79th St., New York.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 1806 Locust St., St. Louis, Missouri.
*1886. Osler, Wm., Oxford University, England.
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1904. Pearce, R. M., 338 East 26th St., New York.
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1905. Riesman, David, 1715 Spruce St., Philadelphia.
1907. Rosenau, M. J., Department of Hygiene, Harvard Medical School, Boston, Mass.
1893. Rotch, T. M., 197 Commonwealth Ave., Boston.
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1887. Starr, M. Allen, 5 West 54th St., New York.
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1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
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1899. Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

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1888.	1910.	Bridge, Norman, 217 S. Broadway, Los Angeles, Cal.
1886.	1897.	Chew, Samuel C., 215 West Lanvale St., Baltimore.
1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
1888.	1906.	Danforth, I. N., 905 West Monroe St., Chicago, Ill.
1886.	1907.	Delafield, Francis A., 5 West 50th St., New York.
1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A., Brimfield, Mass.
1886.	1900.	Guitéras, John, Havana, Cuba.
1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, Rush Medical College, Chicago.
1886.	1908.	Henry, Frederick P., 1635 Locust St., Philadelphia.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1889.	1904.	Loving, Starling, 229 East State St., Columbus, Ohio.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1887.	1905.	Meigs, Arthur V., 1322 Walnut St., Philadelphia.
1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
1891.	1905.	Smith, Andrew H., 18 East 46th St., New York.

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1887.	1902.	STARR, LOUIS, 1818 S. Rittenhouse Square, Philadelphia.
1886.	1907.	STERNBERG, GEORGE M., 2005 Massachusetts Ave., N. W., Washington.
1886.	1906.	TRUDEAU, EDWARD L., Saranac Lake, N. Y.
1889.	1904.	WALCOTT, HENRY P., 11 Waterhouse St., Cambridge, Mass.
1886.	1908.	WOOD, HORATIO C., 4107 Chester Ave., Philadelphia.

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* Honorary Members.

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1886. Atkinson, I. E., Baltimore.
1886. Ball, A. Brayton, New York.
*1890. Barker, Fordyce, New York.
*1886. Bowditch, Henry I., Boston.
1886. Bruen, Edward T., Philadelphia.
1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1886. Donaldson, Frank, Baltimore.
1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
*1886. Folsom, Chas. F., Boston.
1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Aiken, S. C.
1886. Graham, J. E., Toronto, Canada.
1886. Howard, R. Palmer, Montreal, Canada.
1886. Hudson, E. Darwin, Jr., New York.
1886. Hutchinson, James H., Philadelphia.
1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
1886. Johnston, W. W., Washington, D. C.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
1886. Loomis, Alfred L., New York.
1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada.
1886. McBride, Thomas A., New York.

Date of Election

*1886. Metcalfe, John T., Cold Spring, N. Y.
1886. Miles, F. T., Baltimore.
1886. Minot, Francis, Boston.
1898. Packard, Frederick A., Philadelphia.
1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
1886. Ross, George, Montreal, Canada.
1886. Schmidt, H. D., New Orleans.
1886. Sinkler, Wharton, Philadelphia.
1905. Steele, J. Dutton, Philadelphia.
1896. Stewart, D. D., Philadelphia.
1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
1886. Thacher, James K., New Haven, Conn.
1886. Whittaker, James T., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS.

CONSTITUTION.

As Amended May 3, 1910.

ROYAL SOCIETY OF MEDICINE
20 MAR
1911

Article I.

Object and Name.

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II.

Members.

The number of active members shall be limited to one hundred and thirty-five. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III.

Officers.

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV.

Duty of Officers.

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V.

Council.

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate,

and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI.

Meetings.

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the Transactions as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII.

Quorum.

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

Article VIII.

Election of Members.

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting

of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX.

Annual Dues.

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X.

Amendments to the Constitution.

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES.

OF THE

TWENTY-FIFTH ANNUAL MEETING.

Held in Washington, D. C., May 3, 4, and 5, 1910, as a part of the Congress of American Physicians and Surgeons.

The following members were present during the meeting:

A. C. Abbott,
J. J. Abel,
J. G. Adami,
S. S. Adams,
I. Adler,
E. R. Baldwin,
L. F. Barker
H. M. Biggs,
F. Billings,
J. S. Billings, Jr.,
A. D. Blackader,
G. Blumer,
B. M. Bolton,
C. S. Bond,
J. W. Brannan,
H. Brooks,
R. C. Cabot,
C. Cary,
H. A. Christian,
T. A. Claytor,
S. S. Cohen,
R. I. Cole,
J. Collins,
W. M. L. Coplin,
J. C. DaCosta, Jr.,
C. L. Dana,
G. Dock,
D. L. Edsall,
H. C. Ernst,
A. A. Eshner,
J. Ewing,
F. G. Finley,
R. H. Fitz,
S. Flexner,
F. Forchheimer,
R. G. Freeman,
J. Friedenwald,
M. H. Fussell,
T. B. Futcher,
H. C. Gordinier,
C. L. Greene,
J. P. C. Griffith,
S. McC. Hamill,
W. F. Hamilton,
H. A. Hare,
J. B. Herrick,
A. W. Hewlett,
L. E. Holt,
H. Hun,
R. Hunt,
A. Jacobi,
W. B. James,
E. G. Janeway,
T. C. Janeway,
E. P. Joslin,
A. O. J. Kelly,
F. P. Kinnicutt,
J. J. Kinyoun,
G. M. Kober,
H. Koplik,
H. A. Lafleur
S. W. Lambert,
M. J. Lewis,
E. Libman,
W. T. Longcope,
M. Longstreth,
Frederick T. Lord,
I. P. Lyon,
A. B. Macallum,
M. G. MacCallum,
A. McPhedran,
F. B. Mallory,
S. J. Meltzer,
A. Meyer,
J. L. Miller,
J. K. Mitchell,
J. L. Morse,
J. H. Musser,
W. P. Northrup,
E. L. Opie,
W. H. Park,
R. M. Pearce,
J. H. Pratt,
M. Prince,
T. M. Prudden,
J. J. Putnam,
B. K. Rachford,

M. W. Richardson,
D. Riesman,
M. J. Rosenau,
T. M. Rotch,
R. D. Rudolf,
B. Sachs,
J. Sailer,
H. Sewall,
F. C. Shattuck,
B. W. Sippy,
A. A. Smith,
T. B. Smith,
T. H. Sollmann,
A. Stengel,
G. M. Sternberg,
C. G. Stockton,
A. E. Taylor,
J. S. Thacher,
W. S. Thayer,
W. G. Thompson,
E. L. Trudeau,
J. Tyson,
H. F. Vickery,
S. B. Ward,
Alfred S. Warthin,
G. H. Weaver,
W. H. Welch,
F. F. Wesbrook,
H. U. Williams,
J. C. Wilson,
L. B. Wilson,
C. F. Withington,
F. C. Wood,
J. H. Wright.

Tuesday, May 3.

Morning Session.—The Association was called to order at 10 A.M. by President Hun, who delivered the President's address.

The Treasurer read his annual report, which was referred to an auditing committee consisting of Doctors James and Prudden.

The Secretary presented the following recommendations from the Council:

Resolved, "That for the ensuing year the annual dues shall be as follows: Salaried laboratory workers, $5.00; practitioners, $15.00; associate members, $7.50; and that the transactions of the Association be furnished upon application to 'Emeritus Members' at their cost, *viz.*, $4.00 per volume."

Upon motion of Dr. Meltzer the recommendation of the Council was approved.

The Secretary announced that the Council does not recommend the adoption of the following amendment, as Article II of the Constitution already provides for a class of honorary members, and the insertion of the word foreign is deemed undesirable.

Resolved, That Article II of the Constitution be amended so as to provide for a group of "Honorary Members," by inserting after the second paragraph the following: "Foreign physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and take part in the proceedings."

Upon motion of Dr. Cabot the amendment was not adopted.

The Secretary announced that the Council recommends the adoption of the following amendment:

Resolved, That the first paragraph of Article VI be amended by the insertion at the proper places of the words, "either," and "or in Atlantic City," so that the paragraph shall read, "The Association shall hold an annual meeting either in the City of Washington, D. C., or in Atlantic City, at a time designated by the Council."

Upon motion of Dr. Cohen the amendment was adopted.

The Secretary announced that the Council does not recommend the adoption of the following amendment to the Constitution.

Resolved, That Section 4 of Article VI of the Constitution be amended so as to read as follows: "The President shall have complete charge of and responsibility for the program. The number of papers to be presented at each meeting shall be limited to thirty, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication."

The Council is of the opinion that every member has the right to present the results of his investigation, and that whenever the number of papers is too large to permit of free discussion during a two day's session the meeting might be extended. The Council believes that contributions to the program should be confined to members of the Association, that papers should be presented in abstract at the meeting but published in full in the TRANSACTIONS, and that there should be full opportunity for discussion.

Dr. Cabot moved the adoption of the amendment.

A rising vote being taken, the amendment was rejected.

Dr. Libman read a paper entitled "Observations on the Etiology of Chronic Infective Endocarditis," which was discussed by Drs. Kinnicutt, Herrick, Billings, E. C. Rosenow, and Forchheimer, Dr. Libman closing the discussion.

Dr. Thayer read a paper entitled "The Commoner Type of Functional Cardiac Murmurs," which was discussed by Dr. Sewell.

Dr. Hewlett read a paper on "The Clinical Significance of Transitory Delirium Cordis," which was discussed by Drs. Pratt, James, Cabot, and Adler, Dr. Hewlett closing the discussion.

Dr. Collins opened the discussion on Acute Anterior Poliomyelitis by presenting the epidemiology of the disease. Dr. Sachs discussed the human pathology and Dr. Flexner the animal pathology of the disease. The papers were discussed by Dr. Richardson, and the discussion was closed by Drs. Sachs and Flexner.

Dr. Barker presented a "Lantern Slide Demonstration of Electrocardiograms in Clinical Diagnosis." Dr. James also presented a

"Lantern Slide Demonstration of Electrocardiograms." Dr. Claytor presented a paper entitled "Orthodiagraphy in Diseased Conditions of the Heart and Aorta," illustrated by lantern slides. These papers were not discussed.

Adjournment at 1.15 P.M.

Wednesday, May 4.

Morning Session.—The Association was called to order by President Hun at 10 A.M.

Dr. Rotch presented "A Study of the Development of the Epiphyses of the Hand and Wrist with a View to the Classifying of the Naval Cadets at Annapolis," which was illustrated by lantern slides and discussed by Dr. Dock.

Dr. Warthin read a paper entitled "Congenital Syphilis of the Heart," which was illustrated by lantern slides and discussed by Dr. Adler, Dr. Warthin closing the discussion.

Dr. Stengel read a paper entitled "Cardiac Hemisystole as Illustrated in a Case of Heart Block," which was illustrated by lantern slides. The paper was discussed by Drs. Hewlett, James, and Thayer, Dr. Stengel closing the discussion.

Dr. H. U. Williams read a paper entitled "The Structure of the Sweat Glands of the Skin in Cases of Chronic Nephritis," illustrated by lantern slides, which was discussed by Dr. Warthin, Dr. Williams closing the discussion.

Dr. Opie read a paper entitled "The Relation of Combined Intoxication and Bacterial Infection to Necrosis of the Liver, Acute Yellow Atrophy and Cirrhosis," illustrated by lantern slides, which was discussed by Drs. Meltzer, Welch, Warthin, and A. B. MacCallum, Dr. Opie closing the discussion.

Dr. Joslin read a paper entitled "Metabolism in Diabetes Mellitus," which was discussed by Professor Magnus-Levy, of Berlin, Drs. Theodore Janeway and A. E. Taylor, Dr. Joslin closing the discussion.

Dr. Taylor read a paper entitled "The Interpretation of the Metabolic Defects in Diabetes Mellitus upon the Basis of the Theory of Intracellular Ferment Action." Dr. Opie presented a paper entitled "The Distribution of Protein-digesting Enzymes in the Body and Their Part in some Pathological Processes." Dr. Pratt presented a paper entitled "A Study of the Internal Secretion of the Pancreas." These papers were discussed by Drs. Sewell and MacCallum, Drs. Pratt and Taylor closing the discussion.

Dr. L. B. Wilson read a paper entitled "The Pancreatic Reaction of Cammidge in Relation to Diseases of the Pancreas and Ductless Glands." This paper was discussed by Drs. Kinnicutt and Pratt. Dr. Wilson closed the discussion.

The Association then proceeded to the election of officers, active members, and associate members, with the following result: *President*, F. Forchheimer; *Vice-President*, J. George Adami; *Secretary*, George M. Kober; *Recorder*, Solomon Solis Cohen; *Treasurer*, J. P. Crozier Griffith; *Councillor*, George Dock.

Active Members: Albion W. Hewlett, Ann Arbor; E. Libman, New York; Frederick T. Lord, Boston.

Associate Members: Thomas R. Boggs, Baltimore; John Howland, New York; Leo Loeb, Philadelphia; Wilder Tileston, New Haven; Augustus B. Wadsworth, New York.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons, F. H. Williams; *Alternate*, W. S. Thayer.

The following notice from Dr. Trudeau, President of the Congress of American Physicians and Surgeons, was read: "News has just been received that Dr. Howard T. Ricketts, while engaged in an investigation of an outbreak of Mexican typhus fever, has died of the disease in the City of Mexico. Dr. Ricketts had recently been called from the University of Chicago to the Chair of Pathology in the University of Pennsylvania. His death while engaged in investigations for the benefit of mankind calls for some appropriate action on the part of the Congress expressive of his services and heroism.

The President of the Congress would like as many members as possible from each association to meet at 2 P.M. in the Cabinet Room of the New Willard in order to take appropriate action on Dr. Ricketts' death."

Adjourned at 1.20 P.M.

Afternoon Session.—The Association was called to order by President Hun at 2.30 P.M.

Dr. Friedenwald read a paper entitled "Alimentary or Digestive Hypersecretion of the Gastric Juice," which was discussed by Dr. Sippy, and the discussion closed by Dr. Friedenwald.

Dr. Sollmann read a paper entitled "Some Reactions of the Vasomotor Centre." No discussion.

Dr. Abel read a paper on "The Behavior of Certain Organic Com-

pounds of Antimony and Arsenic in the Treatment of Experimental Nagana, Dourmé, and Surra." No discussion.

Dr. Meltzer read a paper on "The Pathology and Treatment of Asthma." No discussion.

Dr. Theobald Smith read a paper entitled "Further Experiments on the Prevention of Active Immunity in Guinea-pigs by Mixtures of Diphtheria Toxin and Antitoxin." No discussion.

Dr. Holt presented a paper on "The Bacteriology of Acute Respiratory Infections as Determined by Culture from the Bronchial Secretion," which was discussed by Drs. Lord, Thayer, and Park, and the discussion closed by Dr. Holt.

Dr. Adami opened the discussion on "Vaccine Therapy" with a paper on "The General Principles Underlying this Treatment." Dr. Richardson discussed "Vaccine Therapy in Typhoid Fever;" Dr. Weaver discussed this treatment in "Streptococcus Infection;" Dr. J. C. Da Costa, Jr., presented a "Report of the Inoculation Department of the German Hospital of Philadelphia," and Dr. Park discussed "The Results of Vaccine Therapy." These papers were further discussed by Drs. Frank Billings and Kinnicutt.

Dr. W. G. Thompson presented "A Clinical Study of Trichinosis," which was discussed by Dr. Cabot.

Dr. T. C. Janeway read a paper entitled "The Resistance to Compression of the Arterial Wall," which was not discussed.

Adjourned at 5.45 P. M.

Thursday, May 5.

Morning Session.—The Association was called to order by President Hun at 10 A.M.

Dr. Herrick read a paper on "Peculiar Sickle-shaped Forms of Red Blood Corpuscles in a Case of Anemia. Dr. McPhedran presented the history of "A Case of Pernicious Anemia with Remission for Several Years," which was discussed by Drs. Dock, Herrick, Thayer, and Shattuck. Dr. McPhedran closed the discussion.

Dr. Christian read "A Report of the Study of Experimental Cardiac and Renal Lesions," which was not discussed.

Dr. Hamill read a paper entitled "The Frequency and Significance of Albumin in the Urine of Normal Children," which was discussed by Drs. Meltzer and Greene.

Dr. Rudolf presented "A Clinical Method of estimating the Coagulability of the Blood," which was not discussed.

Dr. Sewell presented "A Preliminary Note on Medical Use of Rectal Infusions," which was not discussed.

Dr. Brooks read a paper entitled "The Effects of Concentrated Salines on the Human Body," which was discussed by Dr. Meltzer, and Dr. Brooks closed the discussion.

Dr. Riesman read a paper entitled "Acute Toxemic Jaundice," which was discussed by Drs. Thayer and Meltzer.

Dr. Northrup read a paper entitled "Five Full Days of Suppression of Urine," which was discussed by Drs. Fussell, Meltzer, Thayer, Shattuck, Rudolf, and Kinnicutt, Dr. Northrup closing the discussion.

The following papers were read by title:

"Protein Fever," V. C. Vaughan, Sr.

"A Study of Experimental Conditions of Low Blood Pressure of Non-traumatic Origin," R. M. Pearce and A. B. Eisenbrey.

"Dilatation of the Aorta," T. McCrae.

"The Effect of Permanent Constriction of the Splanchnic Arteries and the Association of Cardiac Hypertrophy with Arteriosclerosis," W. T. Longcope.

"An Experimental Study of the Influence of Digitalis on the Heart and Vessels," H. A. Hare and A. G. Ellis.

"The Treatment of Aortic Aneurysm by Wiring and Electrolysis," A. A. Eshner.

"Two Cases of Pernicious (Addisonian) Anemia," C. N. B. Camac and Lindsay S. Milne.

"Clinical Studies in Amebic Dysentery," George Dock and R. Lyons.

"Later Note on Physical Exploration and Treatment of Heart Disease, with a Final Word upon Operations and Heart Failure," B. Robinson.

"On the Presence in the Urine after Anesthesia of a Substance not Acetone, Giving the Common Test for Acetone," A. E. Taylor.

"Observations on Intestinal Infantilism," C. A. Herter.

"A Note on the Effect of Feeding Fermented Corn to Monkeys," C. A. Herter.

"A Case of Splenomegaly with Marked Anemia of a Pernicious Type," R. D. Rudolf.

"A New Method for Counting Blood Platelets," J. A. Wright and Roger Kinnicutt.

Adjourned at 12.45 P.M.

GEORGE M. KOBER,
Secretary.

ADDRESS OF THE PRESIDENT.

By HENRY HUN, M.D.,
ALBANY, N. Y.

During the last year our Association has lost by death one from each of its classes of membership—emeritus, active, and associate.

Dr. Andrew H. Smith had been a member since 1891, and in 1905, toward the close of a long, active, and honorable medical and literary life, he entered on the emeritus list and did not afterward participate in our proceedings.

Dr. Wharton Sinkler was one of our original members, and was still in full activity, rounding out a useful and brilliant life, crowded full of the best kind of both public and private professional work.

Dr. J. Alison Scott was one of our associate members, whose work already done gave promise of an unusually successful medical career.

Surely it can be said of all three of these men, "Well done, good and faithful servants."

This, our twenty-fifth annual meeting, seems a fitting time for your President, with his three and twenty years' experience as a member of the Council, to look back over the quarter of a century which constitutes the life of the Association and to seek in the experience of its past some suggestions to guide its future and to judge how fully we have been able to fulfil that inspiring prophecy of Dr. Delafield, made at the first meeting, when he said: "We want an association composed of members, each one of whom is able to contribute something real to the common stock of knowledge. We want a society in which we can learn something, to which we may

come year after year with the well-founded hope that at each meeting we shall find something to learn."

Have we, then, succeeded in gathering together such a membership? We may say, without boasting, that we have been so successful in our selection of candidates that membership in the Association still remains a high honor and privilege, to be obtained only by scientific achievement. Doubtless mistakes have been made, but coalitions to elect members on account of college affiliations, or of race, or even of friendship, have been little in evidence.

The wise selection of a few men out of a long list of worthy candidates is a difficult and disagreeable task. But, if the Association is to maintain its high position, the best men must be elected and less fit men must be rejected in spite of the promptings of friendship or of self-interest. It sometimes happens that nominees are personally unknown to any member of the Council. Therefore, it is the imperative duty of each member to write to the Secretary concerning those nominees with whom he is personally acquainted. It may seem needless to say that such letters should not be the outcome of friendly solicitation, but should be spontaneous and should be dictated by the definite knowledge of the scientific productivity of the candidate. When a man is proposed whom any member deems undesirable, it is especially important that letters should be written, frankly stating why the nominee would probably not make a desirable member. Such letters have the largest influence upon the Council and are of the greatest value in preserving a high standard of membership. This duty of writing commendatory or critical letters may be pleasant or may be disagreeable, but it is a service which each member owes the Association in order to preserve it from deterioration.

Our membership is now practically full and there is a long waiting list, yet there seems to be no necessity of increasing our numbers at present, although in the near future it will probably be desirable to do so. But an increase of membership will certainly render the program problem, already acute, even more difficult.

We have been no less successful in our scientific achievements than in our selection of members. While epochal discoveries are not frequent, each year our program has represented the very highest

achievements in medical research throughout the United States and Canada.

With a membership of active investigators, naturally many papers are offered each year. This is the expression of the vigorous life of the Association. We do not need to solicit papers, we are overwhelmed by them. How shall we find time to listen to them all? We *must* hear of the work of our active members. We wish to hear the same of our associate members, and also to judge of their qualifications by a personal hearing and a questioning of their work.

We cannot well restrict the material offered. Every member is of such prominence in the profession that we should not refuse to listen to him. If the papers are to present the most recent advance in medicine, they are rarely finished before the date of meeting and could not be submitted to a Program Committee beforehand, even if any Committee would be willing to perform the ungrateful task of accepting and rejecting papers of the high order presented to our Association.

We have been considering this problem for several years, and after talking with many colleagues I am convinced that the only practical solution is, first, to limit the contributors to actual members, unless in very exceptional cases; secondly, to have the essentials of each paper presented in as brief an abstract as is compatible with clearness; thirdly, to promote full discussion; and fourthly, to extend the meeting over sufficient days or sessions to permit the presentation of every paper offered. Formerly our meetings extended over three days, as is still the case in many associations, and this limit, I think, we shall never need to exceed. Members unable to attend the whole meeting could select their days.

Finally, as each one of us looks back over the past meetings, he must, I think, feel that their special charm has lain not in the scientific program, but in the inspiration he has often received from a few intimate words with the great leaders of our profession and in the conversations he has held with his colleagues working in the same or allied fields in different parts of the country. Dr. Fischel told me that the great Master Virchow once said to him in Kroll's Garden in Berlin, "My friend, I have learned infinitely more from short conversations with colleagues at a small table drinking beer than from all my scientific societies."

In a word, the social side of our meetings is of great influence and value. I think, further, that all our old members will agree that in our early days of small beginnings this social factor was greater than it is at present. Like the New Willard Hotel, Washington has grown so large during the last quarter of a century, and presents so many distractions, that we lose touch with our members in these days.

It is for this reason that I hope the experiment may be tried of holding our meetings occasionally in Atlantic City, where we can all live together under the same roof and can be in constant communion with each other during the entire two or three days and evenings of the meetings, and so, perhaps, we may recover, in some measure, at any rate, that old social charm which seemed so alluring to us older members.

The Association of American Physicians gave me the privilege of service as its Secretary for one and twenty years, the best years of my life; and in electing me your President you have conferred upon me that which is, and must ever remain, my highest professional honor. For these marks of kindness and good-will I thank you.

OBSERVATIONS ON THE ETIOLOGY OF SUBACUTE INFECTIVE ENDOCARDITIS.

By E. LIBMAN, M.D., and H. L. CELLER, M.D.,
NEW YORK.

During the last eight years we have had the unusual opportunity of making studies in 43 cases of subacute infective endocarditis. Some of these cases were seen in the wards of Mount Sinai Hospital, with the kind permission and coöperation of the attending physicians (Drs. Brill, Koplik, Manges, Meyer, and Rudisch). Many of the cases were seen in the private practice of ourselves or of other physicians who kindly called us in to make bacteriological studies, or to see the cases clinically. In 36 of the 43 cases, blood cultures were made during life. Of the 43 cases, 29 were seen since 1906; this shows that the disease is now being more frequently recognized. In many of the cases we were enabled to make not only bacteriological, but also clinical, therapeutic, and pathological studies. The details of these investigations, together with a discussion of the literature of the disease and the question of terminology, we shall reserve for a subsequent comprehensive presentation.

The duration of our cases varied from four months to a year or a year and a half. The longer cases may be grouped as the chronic type. Although the cases differed from each other in certain respects, the picture as a whole is a characteristic one, resembling that described by other writers on the disease.[2 3 4 5 6 7 8] In nearly all the cases the disease began insidiously; it was often difficult to determine with any degree of accuracy the date of onset. Fever was present in all the cases, at times quite low, at times (usually later in the disease) high and intermittent, with or without chills. In the cases in which splenic infarctions dominated the clinical

picture the temperatures were usually high and markedly intermittent. Malaise and gastric or intestinal disturbances were frequently present; sweats occurred in nearly all the cases, usually during the latter part of the disease. In all of the cases there was progressive weakness and emaciation.

The spleen was nearly always enlarged and palpable. Pains were quite a constant feature. In some cases they were localized in the bones, joints, or muscles, in others they seemed to be neural in origin. Mild joint swellings were not infrequently met with. At times the pains were due to the development of embolic aneurysms,[1] which are so apt to occur in the course of the disease under discussion. The painful erythematous cutaneous nodules, the diagnostic value of which has been particularly emphasized by Osler, seem to be pathognomonic. A symptom to which no attention has been paid is the tenderness of the lower part of the sternum that was present in nearly all of our cases. It is present at times even before the anemia is sufficiently developed to account for it.

The progressive anemia of the disease and the color of the face (waxy, dirty waxy, or whitish) are noteworthy features. The leukocytes were not usually increased to any degree except when the disease was advancing and various secondary lesions occurred. Petechiæ occurred in nearly all of the cases at some time or other. At times they were abundant, and were scattered over a large part of the body. At other times they were few in number and but few crops appeared. Hematuria, microscopic or macroscopic, occurred quite commonly.

None of the cases that we succeeded in following recovered. We performed autopsies in 19 cases. In 15 of these blood cultures had been made during life; in 1 of these 15 cases the cultures were all negative (5 were made).* The process was always engrafted on a previously diseased valve, and the history nearly always pointed to earlier attacks of rheumatism. The lesion was vegetative in type, not ulcerative. When the aortic valve was involved, there was a

* After this patient left Mount Sinai Hospital he was admitted to the Sydenham Hospital. Several blood cultures made there were also negative. A postmortem examination was made and the lesions typical of subacute infective endocarditis were found. The vegetations showed masses of streptococci; no cultures were made. We are indebted to Dr. B. S. Oppenheimer for these facts.

marked tendency for the process to spread down and attack the wall of the ventricle, the ventricular surface of the aortic flap of the mitral valve, and the chordæ tendineæ. If the mitral valve was involved, the process spread over the wall of the left auricle and involved the chordæ tendineæ. The latter were often torn. At times the auricular lesion was much more extensive than the valvular lesion. This accounts for the fact that in many cases the cardiac auscultatory phenomena change so little during the course of the disease.

The distribution of the lesions was as follows: In ten cases the mitral valve alone was implicated; in all of these there was auricular endocarditis. In 2 cases the aortic valve alone was involved. Both valves were affected seven times. In 6 of these auricular endocarditis was present (in one no note is recorded as to whether there was such a lesion or not). It is evident that a lesion of the auricle practically always occurs when the mitral valve is involved. In one case, that of a man dying of decompensation and chronic nephritis, changes were found that indicate that the lesions in subacute infective endocarditis may heal at least to a certain extent. The characteristic lesions were found on the auricular wall, undergoing organization; the chordæ tendineæ showed the usual lesions, undergoing fibrous and calcareous changes. There were no bacteria in the blood nor in the vegetations. As a rule, the vegetations in this disease contain innumerable organisms.

As stated above, we have encountered 43 cases which were characterized by the clinical course and the pathological findings just detailed,* and in 36 of these cases blood cultures were made.† Altogether 103 examinations were undertaken.‡ In 35 cases we found the atypical cocci which we shall presently describe. In one case we found the influenza bacillus. In this case the clinical course and pathological findings were essentially the same as in the large group in which cocci were found. Even the typical, painful, erythematous nodules were present. The blood plates in the case

* The spleen and kidneys also show typical lesions which we will not now describe.

† Two cases are still under observation.

‡ We do not include a few cases which were studied bacteriologically after death only, because ordinary bacteria may cause a secondary or terminal infection in cases due to the atypical cocci and crowd the latter out.

were remarkable in that the hemoglobin was attracted, as it were, to the colonies. For the colonies became deep red after a few days, and the rest of the plate became lighter in color. The number of colonies found in this case was at first 53 to the cubic centimeter; later it rose to 94.

In the cases due to infection by the atypical cocci there was a great variation in the number of organisms present. In one case only two colonies were found in 25 c.c. of blood. The largest number was 500 in a cubic centimeter. It is noteworthy that in a few cases it was found necessary to make several cultures before a positive result was obtained. And we encountered one case (mentioned above) in which 5 cultures made in many media were all negative. Drs. Fried and Sophian, of our laboratory staff, made a microscopic study of the blood in a number of cases,* and found that this gave no definite information in cases which at the time gave negative cultural results.

We were recently surprised to find that it is at times necessary to observe the plates for six days. We had usually kept them for five days. The probability is that this accounts for some of the negative results. As a rule, the organisms can be found after forty-eight hours, at times after twenty-four hours. It is advisable to use both fluid and solid media.[9] Media containing glucose at times gave a better result. Serum-glucose-agar was often found to be the optimum medium.

Before proceeding to describe the cocci found in our cases, it is necessary to discuss briefly the character of pneumococci and streptococci, which they resemble. Based on the studies of Dr. Buerger,[10] we had for several years made use of certain criteria for the identification of these organisms. When Neufeld's[11] publication appeared, claiming that pneumococci and the Streptococcus mucosus were dissolved by bile, and that streptococci were resistant, Dr. J. Rosenthal and one of the writers (Libman) made a study to determine whether this held true according to our classification.† We found that all organisms which were identified as pneumococci or as the

* These results will be published later. They constitute a part of a large study of the blood for bacteria by direct microscopic examination.

† Paper presented at the meeting of the Association of American Pathologists and Bacteriologists in 1908; not yet published.

Streptococcus mucosus were promptly dissolved by bile, and that those identified as streptococci were not. We included in our study a careful observation of the growth of the organisms on the surface of blood plates (the method of differentiation first suggested by Schottmüller).[12]

The earlier studies made in our laboratory by Dr. Buerger had given us the following data. Pneumococci often possess a capsule the morphology of which is diagnostic.[13] At times the capsule degenerates and resembles the one sometimes found on streptococci, or the capsule may be lost. The Streptococcus mucosus also possesses a diagnostic capsule, which, however, may undergo the same changes as the pneumococcus type capsule. Ordinary streptococci often have capsules, but these are not diagnostic, as the degeneration of the capsules of pneumococci or of the Streptococcus mucosus may produce the same form. The pneumococcus ferments inulin (as claimed by Hiss[14]), but not in every generation. The Streptococcus mucosus always ferments inulin,[15] ordinary streptococci rarely do so. Pneumococci and the Streptococcus mucosus were rarely found to throw out a precipitate in glucose-serum-agar;* streptococci always do.[16] The pneumococcus often grows in a typical fashion on the surface of serum-agar or glucose-serum-agar (so-called pneumococcus ring colonies[17]). At times pneumococci or streptococci grow mucoid in the media, but otherwise differ in no way from the ordinary forms. These organisms are called mucoid pneumococci and mucoid streptococci.

In the course of the studies made by Dr. Rosenthal and ourselves we investigated 19 strains of pneumococci, 69 of streptococci, and 12 of the Streptococcus mucosus. The organisms were isolated from local infections in various parts of the body.

* In this test 0.5 per cent. glucose is used, and an ascitic serum having a specific gravity of 1015 or more. The time of observation is two days. Dr. Buerger's positive results were obtained only after two days had elapsed.

	Pneumococcus.	Streptococcus.	Streptococcus mucosus.	Endocarditis cocci. A	Endocarditis cocci. B
Capsule	1. Diagnostic or 2. Degenerate or 3. Not present	1. Non-diagnostic or 2. Not present	1. Diagnostic or 2. Degenerate or 3. Not present	Not present	Not present
Gram	+	+	+	+	+
Blood plates	Green; no clear zone	1. Gray, clear zone 2. Green; no clear zone 3. Moist, good white growth, or slight dry whitish growth; no clear zone	Green usually mucoid; no clear zone	1. Green; no clear zone 2. Moist good white growth, or slight dry whitish growth; no clear zone	
Inulin fermentation	+ (occasionally—)	— (rarely +)	+	+	—
Precipitation	— (rarely +)	+	— (rarely +)	+	+
Solution by bile	+	—	+	—	—

Note: Ring colonies of the pneumococcus are diagnostic.

Our investigations led to the following conclusions:

1. The type capsule of the pneumococcus and that of the Streptococcus mucosus, as described by Buerger, are diagnostic. All organisms presenting such capsules are dissolved by bile.

2. Solution by bile is diagnostic of the pneumococcus and the Streptococcus mucosus. This latter organism is easily distinguishable by its type of capsule and certain other features.[1]

3. The absence of precipitation speaks almost absolutely against an organism being a streptococcus.

4. The fermentation of inulin is not of pathognomonic value. While it is a feature of the pneumococcus, the property may be absent, and, furthermore, streptococci occasionally give a positive result.

5. The ring colonies are diagnostic of the pneumococcus.

6. The growth on blood plates* gives the following results of value:

(*a*) A definite large (2 to 3 millimeters in diameter), perfectly clear zone (so-called hemolytic zone) about a colony is diagnostic of streptococci if it is found to persist in several generations. In-

* In this work, besides using human blood plates, we also made use of the blood plates made of ox blood according to the method of Bernstein and Epstein.[18]

complete clearing is of no diagnostic value, nor is a linear clearing. The clearing may occur in concentric rings.

(*b*) Pneumococci always grow green* (once the growth was brownish green). An organism not producing a green color always proved on further study not to be a pneumococcus.

The conclusions we arrived at in the study just detailed were based on the following findings:

1. Type capsules were found on all 19 pneumococci studied, either in the original material (pus, sputum, etc.) obtained from the patient or in cultures. All the organisms were dissolved by bile. Type capsules were found on all the strains of the Streptococcus mucosus. Of 69 ordinary streptococci, 32 had capsules.

2. All of the streptococci precipitated. In one this was slightly marked, but was intense after passage through one mouse. Of 19 pneumococci, only 2 precipitated; these 2 had been in bile (this seems to favor the development of a precipitating power) and did not precipitate in the second generation. Of 12 strains of the Streptococcus mucosus, one precipitated for four generations, and one for two generations.

3. Of 19 pneumococci, all fermented inulin except 2 (in 2 others the result was very slight). With these 2, a slight result was obtained by passage through two mice. The strains of the Streptococcus mucosus all fermented rapidly. Of the 69 streptococci, 2 fermented inulin; 1 lost the property in the second generation and also after passage through one mouse. The other lost the property after passage through two mice.

4. On blood media, all but 11 of the streptococci grew in fine gray colonies surrounded by an absolutely clear zone (as described by Schottmüller for the Streptococcus longus). Of the 11 exceptions, 7 gave a good, white, moist growth without any clear zone,† 3 grew green like the pneumococcus, and 1 gave only a slight almost colorless dry growth with no clearing.

All the pneumococci grew in green colonies, some with partial clearing, some with no clearing. Some colonies were green by

* In our work we included, as producing green color, organisms the colonies of which either were green or were surrounded by a green zone.

† These would correspond, at least in part, to the type called Streptococcus mitior or viridans by Schottmüller.

transmitted light (not by reflected light). One produced brownish-yellow-green colonies, and one produced clear zones about the colonies in a plate made with the blood of the patient from whom the organism had been isolated, but not on other blood plates. All of the strains of the Streptococcus mucosus produced green colonies and were mucoid in the earlier generations.*

The strains of ordinary streptococci which grew white were obtained as follows:

Three were from cases of otitis media and mastoiditis, one from a case of cholecystitis, one from a case of liver abscess, and one was a postmortem invader.

The streptococcus which gave a slight dry growth was obtained from a skin infection. The 3 strains that gave green colonies were obtained as follows: One from a case of appendicitis, one from a case of otitis media, and one from a specimen of sputum.

The cocci found in the cases of subacute and chronic infective endocarditis during the last few years were carefully studied along the lines we have just discussed. These organisms are all Gram positive. They have never been found to have a capsule. They are either round, ovoid, lancet-shaped, or bacillary in form, and may be found in diplococcus form, in groups or in chains. Every organism except one was found sooner or later to grow in chains, which were often long and convoluted. They are usually smaller than the ordinary streptococci and pneumococci, and grow more poorly, especially when first isolated. We shall not now describe their manner of growth on the ordinary laboratory media (gelatin, agar, potato, milk, etc.) because no definite diagnostic criteria are thus afforded.

As will be seen by looking at the chart, these organisms fall into two groups, one of which ferments inulin and the other does not.† The former comprises about one-third of the organisms. They all produce a precipitate in serum-glucose-agar and are all resistant to the action of bile.

* In the paper to be published by Rosenthal and Libman the growth of the Streptococcus mucosus and of the pneumococcus will be described in more detail. A very interesting type of growth not hitherto noted was seen a number of times.

† A study of the growth on other carbohydrates gave no useful differential features except when raffinose was used. The organims can probably be further subdivided by a study on raffinose media. The inulin and raffinose fermentation generally go hand in hand. Twice we found organisms that fermented raffinose and not inulin.

In describing the growth of these cocci on blood plates a distinction must be drawn between the phenomena seen in the plates made with the patient's blood and in subsequent inoculations on plates made with other blood. In the former, a definite clear zone is sometimes, although rarely, seen. It usually takes two to four days to develop. (Ordinary streptococci that produce a clear zone do it more rapidly.) In subsequent transplantations this is lost. The colonies in the original plates are usually white in color with or without a green or an opaque zone about them. The deeper colonies are white or opaque. In subsequent cultures on blood plates three types of growth are seen. There may be a production of green pigment, there may be a moist white growth, or a dry, almost colorless, very slight growth.

Before finally coming to the question of the grouping of these organisms, it is essential to draw attention to the remarkable changes which pneumococci (and to a much less extent streptococci) may undergo in the body, especially in the blood current. Studies made by Drs. Buerger and Ryttenberg[19] demonstrated that pneumococci may lose their type capsules, may lose the property of fermenting inulin, and may acquire the power of precipitation. One of the writers had previously shown that they could acquire temporarily the property of producing a clear zone about the colonies.[20]

By inoculation of such cultures into mice, the method usually employed in an attempt to bring back the features of altered pneumococci, some organisms could be converted into typical pneumococci. However, if such organisms were first kept in media for a long period and then inoculated into mice, the pneumococcus characters could no longer be developed,* that is, the organism retained the power of precipitation, did not regain the power of fermenting inulin, nor regain the capsule. As regards streptococci, we have already stated that in the work done with Dr. Rosenthal we found two that fermented inulin and lost the property after passing through mice. We did not find any streptococci that lost the power of precipitation, and the streptococci that produced clear zones about the colonies retained this property indefinitely.

* Studies with bile were not made by Drs. Buerger and Ryttenberg, the test not then being known. Nor were blood-plate studies made.

It will now be of interest to compare the endocarditis cocci with pneumococci and streptococci. Except that they are smaller and grow more poorly (unimportant points when it comes to a question of classification), the group that does not ferment inulin resembles the type of streptococci which produce no zones of clearing in blood plates. Of course, the real relationship of these streptococci to the ordinary streptococci that produce à clear zone on blood plates has not been definitely determined. The inulin-fermenting group might be considered to be a separate type, or might be regarded as being the same as the others except that they acquired the property of fermenting inulin in the body and permanently retained the property.* But we have no proof, as yet, that this may occur.

At first sight these organisms, especially those that do not ferment inulin, would appear to be far removed from pneumococci. But we have seen that pneumococci may lose their capsules, may lose the property of fermenting inulin, and may acquire the property of precipitation. Many of the organisms grow on blood plates like pneumococci. But we have not hitherto isolated pneumococci from the body that were resistant to the action of bile. If we should meet with such pneumococci, we could more easily suspect that the organisms under discussion are altered pneumococci. Possibly they represent more than one type of organism.

The features of the endocarditis cocci have remained constant in subinoculations carried over a long period of time (in some instances as long as eighteen months). Every organism that fermented inulin still does so. After repeated animal inoculations (mice, rabbits) no change in the important characteristics has been demonstrated. Capsules have never been developed. We have made studies of the agglutinative power of sera from patients and of sera of animals immunized by repeated injections of the cocci, but we have thus far not found any agglutination of pneumococci or streptococci.† Studies made by Dr. Fried of the opsonic power of the serum of patients or of immunized animals have given no definite results.

* There was no relationship found between the type of growth on blood media and the occurrence of inulin fermentation.

† These studies were carried out in association with Dr. A. Sophian.

Nor have the studies made up to the present time by Dr. Kaliski and Dr. A. Sophian by means of complement fixation tests.*

We might add here that the organisms are not, as a rule, very pathogenic for animals. In mice we have sometimes produced peritonitis by intraperitoneal inoculations. In rabbits we have succeeded in producing peritonitis, and several times have produced endocarditis. In one instance, as you will see from the specimen, the vegetations almost blocked the aortic orifice. Endocarditis resulted from our experiments in a much smaller proportion of the inoculations than in those of Rosenow.[6] This held true even after we adopted the same methods as were used in the work of this observer.

Let us now glance at the results obtained by other observers in subacute infective endocarditis, in order to ascertain what organisms they found and whether any of the organisms were the same as those which we encountered. An accurate comparison is not possible because no two authors have made use of the same methods in studying the organisms.

Lenhartz,[2] in 16 cases, found streptococci 13 times, a staphylococcus, a pneumococcus, and a gonoccoccus, each once. He says that in 10 of the 13 streptococcus cases the organism was small. He calls it the "Streptococcus parvus." No further characteristics are given. We believe that some of his organisms must be the same as some of ours because they are found in the blood in the same type of disease.

Osler[4] describes 10 cases, in 6 of which blood cultures were made. Three of these gave a negative result, 1 revealed a streptococcus, and 1 a staphylococcus.

Horder[5] in a very extensive study of various forms of infective endocarditis describes 13 cases, from 9 of which he isolated streptococci, and from 4, influenza bacilli. He identifies these streptococci with "Streptococcus salivarius" and "Streptococcus fecalis," two of five groups into which Andrewes and he[21] had classified streptococci (the other three groups are Streptococcus pyogenes, Streptococcus anginosus, and the pneumococcus). This classification is based mainly on the differences in the power of different streptococci

* These studies will be continued, as only positive results will be of definite value.

to ferment various carbohydrates. But some earlier work done in our laboratory[22] and some recent studies on this subject by Dr. Sophian and ourselves indicate that the classification of these authors cannot be adopted. Whether Horder's organisms are the same as ours it is not possible to say, because the methods of study used by him and by us differ. Considering that the clinical course was the same as in our cases, the organisms may very well have been identical. It is of interest in connection with our results to note that he found not only organisms classed as streptococci, but also influenza bacilli in the blood of his cases.

Rosenow,[6] in a contribution to the bacteriology of this subject replete with interesting and valuable data, to only a few of which we can now refer, states that he found pneumococci in all the cases that he studied. "When the organisms were first isolated in broth they grew in clumps and produced a diffuse turbidity slowly, and upon agar slants the colonies grew more or less tightly to the surface. The stained specimens gave diplococcus forms and chains. The chain formation as well as the property of growing in clumps in broth and of adhering tightly to the surface of blood-agar slants disappeared after cultivation for a variable period. . . . By cultivation on artificial media all the strains change gradually into typical lanceolate diplococci, often capsulated, growing as typical pneumococci in broth and on blood-agar slants. On animal inoculations this modification often occurred abruptly." The agglutination and opsonic studies of Rosenow do suggest a relationship of his organisms to pneumococci, but until the organisms are shown to have definite pneumococcus character, we would hesitate before surely classing them as such.

Through the kindness of Dr. Rosenow, we were enabled to study five of his organisms (Nos. 292, 293, 362, 409, 413). We have not yet finished a comparative study of his organisms and ours. Only one of the organisms now produces a green color on blood plates, and that is very slight. One organism (409) ferments inulin regularly; all of the organisms are insoluble in bile. Capsules cannot be demonstrated by us. As regards chain production (on which we are not willing to lay any great stress in diagnosis) it could be observed in the growth of all the organisms in fluid media. Three

of the organisms precipitate markedly, two slightly. One of the organisms that precipitates actively (409) is also an inulin fermenter.

Schottmüller,[8] in a recent publication, describes under the name "endocarditis lenta" the clinical features of subacute infective endocarditis. He cites 5 cases, in the blood of all of which he found the organism which he calls the "Streptococcus mitior," or "Streptococcus viridans," because the colonies are those of a poorly growing organism and because they produce a green pigment on blood plates.

It will be remembered that Schottmüller[12] classed the streptococci (apart from the Streptococcus mucosus) into two groups, according to the manner of their growth on blood plates and in blood bouillon.* The one type is the "Streptococcus longus," which grows in fine gray colonies and produces a marked clearing of the media; in blood bouillon it produces a carmine or Burgundy red color. The other, the Streptococcus mitior or viridans, which grows slowly, develops fine gray or black green colonies, and produces no clearing; in blood bouillon it produces a brownish-red discoloration. No data are given as to inulin fermentation, precipitation, or the reaction with bile, three of the criteria which we consider of importance. It is, of course, very likely that Schottmüller's organisms are the same as ours. He believes that the organism is specific for subacute infective endocarditis. With this conclusion we cannot agree, as we have also found influenza bacilli in the blood in one such case, and Horder described four such cases.

We have shown the difficulties that are encountered in an attempt to properly classify the organism which we have met in our cases. We have also shown that organisms which are practically the same as the group which does not ferment inulin have been found by us in local infections of various kinds. The important point to be brought out is that up to the present time whenever we have found the organisms which we have usually called endocarditis cocci par excellence (or attenuated streptococci of endocarditis) there was always present an infection of the endocardium. In no other disease have we found these organisms in the blood current. They, there-

* Schottmüller also describes differences in the manner of growth in milk and bouillon, but, as stated before, these phenomena cannot be depended upon for definite differentiation of organisms in the streptococcus-pnuemococcus group.

fore, as Schottmüller also believes, seem to have diagnostic import. Our studies on the bacteriology of the blood now comprise over 3000 blood cultures, made in the last twelve years. Our attention was first drawn to the fine colonies of the endocarditis cocci by Dr. M. Gershel, then an interne, in 1902. In the following year Schottmüller drew attention, in the publication already cited, to his "Streptococcus mitior." Since 1902 we have made 2750 blood cultures. Many cases of acute endocarditis were studied in which ordinary streptococci, staphylococci, pneumococci, and the gonococcus were found. But these organisms have not thus far been encountered in any blood culture made in the type of endocarditis to which this paper is devoted.* Some of these cases present such a typical symptom complex that a clinical diagnosis can be made with a fair degree of certainty. It may, however, be difficult to differentiate them from cases of chronic endocarditis with fever in which there is no superimposed bacterial infection of the valve, and the disease is not infrequently confused with such conditions as rheumatism, typhoid fever, tuberculosis, Banti's disease, or splenic anemia.† While the onset is usually insidious and an acute factor does not develop for a long time (or possibly not at all), there are cases which first present themselves with a picture resembling an acute surgical condition. Under these conditions the disease has been mistaken for appendicitis (because of acute abdominal symptoms), for abscess of the spleen, or for pyelonephritis. And it has transpired that surgical measures have been adopted in such cases.

As we have already indicated, we have thus far found no help in diagnosticating the disease by microscopic study of the blood, by opsonic, agglutination, or complement fixation tests. The absolute diagnosis must, for the present, rest on the cultural study of the blood.

* The accurate characterization of these organisms will be of value in studying the source or sources of infection.

† Cf. Schottmüller. In one case a clinical diagnosis of tuberculous kidney was made because of the marked renal phenomena.

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DISCUSSION.

Dr. Francis P. Kinnicutt: As I understand Dr. Libman, the prognosis in cases of chronic endocarditis depends largely upon the results of the blood culture. If this disease can be proved to be an infective one, and the organism of the nature he describes, the prognosis must be an extremely unfavorable one. We all are familiar with these cases of chronic endocarditis, the characteristics of which have been so well described by Dr. Osler. There is fever, especially in children, lasting one, two, three, four, or five months, with a temperature curve as described; many of these patients, however, get well. As I understand Dr. Libman, blood cultures permit of a differentiation of these cases and determine the prognosis. If this proves to be correct, a useful means in diagnosis is at our disposal.

Dr. James B. Herrick: I should like to ask Dr. Libman in what proportion of the cases was there a history of valvular lesions having preceded the chronic endocarditis. Also, what relation does the organism he described bear to the so-called organism of rheumatism.

Dr. Frank Billings: My experience with cases of chronic infective endocarditis agrees with that of Dr. Libman in regard to the clinical course of the

disease and the fatality of it. I do not know exactly just how many records of patients we have, but last year we reported 15 cases of this type, and since that time 10 or more. One finds the disease more prevalent than is commonly supposed. I will not attempt to relate the symptoms, because Dr. Libman has already done so. The symptoms are not so very characteristic, because the disease has frequently been mistaken for malaria, for there may be chills, fever, and sweats; again, because of the joint troubles, one is led to look for a subacute form of rheumatism; again, because of the peculiar type of fever, some mistake the disease for typhoid fever, and so on. Among the diseases, however, in which a mistaken diagnosis is most commonly made is tuberculosis. These patients may wander from the city to the country, back again to the city, and again to the country. I have in mind a girl who was sent south for the winter, and who was brought back again and treated all the following summer as an invalid. Another patient from Iowa was constantly treated for rheumatism; she had already been treated for one year for tuberculosis, and the doctor thought that she should be kept out of doors, and should exercise; he made her walk one or two miles a day. These are the sorts of histories one obtains. I do not think, however, that one can make a diagnosis of the condition without taking blood cultures; one may say that he has a case of chronic infective endocarditis to deal with, but one must remember that some of the very important diagnostic sym toms are absent at the beginning of the disease. I recall two cases in which the right heart was involved; there were no petechiæ, the spleen was enlarged, and a diagnosis was made of tuberculosis. The main thing to say, however, is that we have a disease which runs a chronic course and which is often mistaken for other infections. So far as I know no patient has ever recovered; certainly, none among the 25 or more that I know of. Some will improve under rest treatment and sometimes they will improve when the autogenous vaccines are employed. The blood cultures will certainly help us in determining the various forms of endocarditis.

Dr. E. C. Rosenow: I wish to congratulate Dr. Libman upon the splendid character of his work. I am sure that we are dealing with the same disease; although in our studies to differentiate the organism we differ slightly in the smaller details. During the first years of this work I thought I was dealing with the Streptococcus pyogenes. Further studies, however, during the last two years have convinced me that on the contrary I was not dealing with the streptococcus, but really with a modified pneumococcus. From a study of the organism from 40 cases I found that the chains were usually very long; and are made up of distinct elongated often lanceolate diplococci. They never had a capsule. All the strains when grown in blood-agar plates produced green coloration, but never hemolysis. All have fermented inulin at one time or another; some fermented inulin in the beginning lost this property, and later acquired it again. By their further study I have been able to make these organisms revert to the normal type of pneumococcus, both morphologically and in

fermentative properties and, most important of all, in pathogenic properties. For instance, injections of huge doses of these pneumococci, while not likely, may kill an animal promptly by pneumococcemia, and in its blood we find the typical pneumococcus. If the animal, however, does not die for a number of weeks and a second injection is administered, it is very likely to die of a pneumococcemia, but here an atypical pneumococcus is usually found. If the animal lives, or survives the first effects of the previous injections, and later develops an endocarditis and probably a pericarditis, the organism isolated resembles, as a rule, the ones injected. Moreover, the virulence increases as the organisms behave more nearly as typical pneumococci. Prolonged cultivation in ordinary media causes them to grow like the ordinary type; cultivation in normal human serum produces a similar effect. The reason these organisms are not dissolved by bile seems this: non-virulent pneumococci cultivated in the laboratory are not dissolved by bile, whereas the highly virulent organisms are. The virulence of the endocarditis cocci is very low. Enormous doses will sometimes not even make the animal sick; if it sickens, the recovery will usually be very prompt.

From a long series of experiments, which are reported in the *Journal of Infectious Diseases*, it seems that these cocci produce so uniformly fatal an issue by a process of self-immunization against the antibodies of the host rather than by the property of virulence as ordinarily understood.

It does not matter so much to what group these organisms belong, whether they be modified pneumococci or modified streptococci; the point of greatest importance for the clinician is to know that by blood cultures and a study of the organisms isolated, a positive diagnosis and prognosis can be made months before the fatal end. The cocci have properties so characteristic that one is tempted, as Dr. Libman has pointed out, to give them a special name, were it not for the fact that the degree of modification varies according to the length of the clinical course, and that occasionally the same organism is found in conditions other than endocarditis.

Dr. F. Forchheimer: It seems to me that the most important outcome of this discussion has already been referred to; one observer here has isolated a pathogenic organism and another observer has verified his findings in a disease which we have been taught to believe was due to a number of the lower forms of life. If this is correct, then we have made an enormous step forward in the recognition of the disease. I have seen a large number of cases which clinically would be considered under the head of this form of endocarditis. I have had a number of cultures made, and I have found a large number of organisms of the lower forms of life. One of these cases I have referred to several times in previous discussions. I confess that I have had therapeutic results, some of my patients getting well. Evidently, from what has been said this morning by two excellent bacteriologists, we are not dealing with the same form of disease. I must have been dealing with a different form of endocarditis. The work that

has been done by the German observers must be gone over again if what we have learned this morning is true.

Dr. E. Libman: Up to the present time we have found a fatal outcome in every case in which we have found this organism in the blood.

In answer to Dr. Herrick's question, I would like to say that in all the cases which we have observed, this disease has been superimposed upon a previous valvular disease. In cases of rheumatism we had not found any organisms in the blood, but often the condition was superimposed upon endocarditis of rheumatic origin. It can be engrafted also upon an arteriosclerotic valve.

As Dr. Rosenow stated, it is very important to recognize certain characteristics of these organisms. Dr. Rosenow's paper is filled with many valuable data, the discussion of which I cannot enter into at the present time. Our organisms do not agree with his in regard to the question of the fermentation of inulin.

As to the question of other means of diagnosis of the disease, we have made investigations to ascertain whether diagnosis could be made by microscopic examination of the blood, studies of the opsonic or agglutinative properties of the serum, or by the presence of specific antibodies. As I stated before, we have hitherto obtained no definite results by these means. The definite diagnosis must, for the present, rest upon the cultural study of the blood.

A CASE OF SPLENOMEGALY ASSOCIATED WITH A MARKED ANEMIA OF THE PERNICIOUS TYPE.

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AND

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The following case seems worthy of being put on record, as it presents many unusual features. The case has been under observation in London and here during many years, and the history can thus be followed out in a way that is not always possible. The diagnosis offers many difficulties, but if, as seems probable, it be one of pernicious anemia, then in several ways the case is one of great rarity.

Case.—W. P., aged twenty-eight years and six months; single; lead glass worker. Admitted to the Toronto General Hospital on June 12, 1909.

Complaints. Weakness, shortness of breath on exertion, and swelling of the abdomen.

Duration. About four weeks, but, as the history will show, has not been really well for over twenty years.

Family History. Father alive and well. Had rheumatism four times. Mother alive, but delicate. Brothers, two; one died from whooping cough; other healthy. Sisters, none. No history of tuberculosis or syphilis in family. No history of any disease resembling what the patient now suffers from.

Personal History. Born in London, England. Came to Canada many years ago, and has resided here since. Has been a lead glass worker for years. Fairly comfortable surroundings, and always has good food. No venereal history.

Previous Health. Was a small, weakly baby. Had measles at the age of four. When eight years old was in the great Ormond

Street Hospital suffering from "jaundice," and remained there for four months. (Notes of this stay are not obtainable.) At ten years of age was readmitted to the Great Ormond Street Hospital, March 5, 1890, complaining of headache and dull abdominal pain. A summary of his condition then, as given by Mr. R. S. Frew, the Registrar of the Hospital, is as follows: "Very thin boy. Skin, pale lemon color. Conjunctivæ slightly tinged. No eruptions or edema. Lips pale and gums slightly swollen. Tongue pale. Cervical glands enlarged, especially on left side. Temperature, 101°. Abdomen not distended. Prominence in left hypochondrium, reaching to umbilicus and descending on respiration. Spleen reaches to within one and one-half inches of left anterior superior iliac spine. Notch quite evident. Liver palpable below costal margin. Heart not enlarged, but systolic murmurs in all areas and conducted into axilla. Chest normal. Blood: Red cells, 1,000,000; white cells, 18,000; hemoglobin, 12 per cent. March 25, red cells, 1,000,000; white cells, 18,000; hemoglobin 25 per cent. April 1, red cells, 1,625,000; white cells, 26,625; hemoglobin, 25 per cent. April 17, red cells, 1,100,000; white cells, 7750; hemoglobin, 40 per cent. April 28, red cells, 1,700,000; white cells, 10,000; hemoglobin, 40 per cent. Blood smear normal. Diagnosis: Enlarged spleen.

"He was readmitted to the Great Ormond Street Hospital in September, 1890 (aged ten years and nine months).

"Since last discharge has gradually become short of breath; lost color; has pains in head and abdomen; no hemorrhages or vomiting. He is yellowish in color. Temperature, 100°. Glands enlarged along posterior border of left sternomastoid and in left groin. Elsewhere are normal. Spleen much enlarged. Liver not palpable. Systolic murmurs as before. Urine contained no albumin or sugar. Blood: Red cells, 1,111,000; white cells, 10,000; hemoglobin, 25 per cent. September 17, red cells, 2,900,000; white cells, 10,000; hemoglobin, 46 per cent. October 13, red cells, 3,500,000; white cells, 14,000; hemoglobin, 70 per cent. Optic disks normal. Sent to Convalescent Home.

"February 9, 1891. Reported at Out-patient Department. Is paler again. No pain. Spleen reaches to one inch beyond the umbilicus. Blood: Red cells, 700,000; white cells, 21,100; hemoglobin, 19 per cent."

After that was twice an in-patient at the Great Ormond Street Hospital at short intervals. His condition was each time the same, and he always temporarily improved.

The patient next was seen at St. Mary's Hospital, under the care of Dr. (now Sir) John F. H. Broadbent, who writes that he well remembers the case. We are indebted to Dr. M. Mitchell Bird, the Medical Superintendent of the Hospital, for further notes, which are condensed to the following: The patient was admitted on July 23, 1894, now aged fourteen years. He complained of dyspnea, slight cough, marked pallor, and extreme weakness. He stated that his periods of good health had been longer after each course of treatment at the Great Ormond Street Hospital. Had been fairly well for some time before the present attack. He was a pale yellow color. Spleen much enlarged, and liver palpable below the costal margin. Loud systolic murmurs were audible over all the precordium. Blood: Red cells, 800,000; white cells, "not increased;" hemoglobin, 25 per cent.

He was treated with rest, arsenic, and iron, and left the hospital much improved.

For the next fourteen years of his life the patient says that he has been well and has never been laid up nor required medical advice. About a month ago, however, his old symptoms of weakness, dyspnœa, and yellow pallor returned, and he has been very poorly since. A week ago he fainted. He entered the Toronto General Hospital on June 4, 1909.

Condition on admission. Patient is a well-developed man. Skin has a yellow and pallid hue, and the conjunctivæ are distinctly jaundiced. In the folds of the axilla and elsewhere there is considerable pigmentation. The Moro reaction is negative. Temperature, 100.3°, and all through his stay in the hospital there was slight elevation of temperature. The lymphatic glands on the right side of the body are slightly enlarged. (It was on the left side that they were enlarged before, according to the early history.) There is no tenderness over the long bones. No wrist-drop or trophic changes suggestive of lead poisoning.

Alimentary System. The teeth are poor and carious. The spleen is greatly enlarged, reaching to half an inch beyond the umbilicus.

It is firm and free from tenderness. The notch is very evident, and also there is a slight narrow groove across the surface of the organ. Liver is not enlarged. The stools are somewhat clay colored.

Circulatory System. There is some dyspnœa and faintness on exertion. He can lie down in bed. No œdema or cyanosis. The pulse is regular and of medium systolic pressure, but collapses between the beats, suggesting the "water-hammer" type. The heart is not evidently enlarged. Systolic bruits are audible all over the precordium, and there is a loud *bruit de diable* in the neck.

Respiratory System. There is a slight retraction at the right apex, but otherwise the system appears to be normal.

Urine. Quantity normal. It is dark red in color, but does not give the bile reaction with nitric acid. A trace of albumin is present. There is no indican. Many crystals of calcium oxalate, uric acid, and urates.

Nervous System. Normal. Reflexes moderately active. Nothing found in the *fundi oculorum.*

Blood. A marked anemia is present, and the color index is persistently 1 or above 1. The results of numerous examinations are collated in the table on p. 27.

The white cells showed signs of immaturity or a tendency to degeneration. Some large mononuclear forms seemed closely to resemble myelocytes, but their structure was too definite. Many of the polymorphonuclear forms were very small, and a tendency to acid staining was evident; but the chief change in the blood was in the red cells, fully 50 per cent. of the non-nucleated forms showing staining in an atypical tint. Stippling was marked, varying from a few coarse granules to hundreds of coarse or fine ones, so closely packed as to produce a close resemblance to an atypical white cell. The question naturally arises here of whether the lead-working occupation of the patient had anything to do with this; but, as both in pernicious anemia and in splenic anemia such staining is common, this suspicion loses much of its weight. The poikilocytosis of the non-nucleated forms was mainly in regard to size, although many cells were irregular in outline and even rosette in form. Many cells were so destitute of staining as to appear as mere ghosts, with just a faintly staining outline. The nucleated red cells were exceed-

Blood Examinations.

Date.	Hemoglobin.	Red blood cells.	White blood cells.	Nucleated red blood cells.	Differential Counts.	Polynuclears.	Eosinophiles.	Basophiles.	Lymphocytes. Large.	Lymphocytes. Small.	Normoblasts.	Megaloblasts.	Total nucleated red blood cells.
1909													
June 12 . .	28	1,152,000	28,000	10,890		65.40	1.57	1.57	3.77	27.67	11.31	27.60	38.91
June 13 . .	..	1,440,000	25,700	13,261		65.00	2.00	0.60	5.80	26.40	22.25	29.35	51.60
June 14 . .	26	.....	23,900	9,010		63.30	1.60	0.60	7.30	27.20	17.70	20.00	37.70
June 15 . .	28	1,520,000	18,000	5,997		63.70	3.20	1.60	4.16	27.20	16.33	17.00	33.00
June 16 . .	31	1,750,000	14,800	5,097		58.36	4.73	1.26	5.04	36.00	.....	.....	34.44
June 17 . .	34	1,724,000	14,000	5,250		60.00	1.90	2.52	2.52	32.70	15.40	22.10	37.50
June 18 . .	38	1,824,000	16,000										
June 19 . .	40	1,856,000	12,000	3,624		62.42	3.18	2.20	4.80	27.07	12.40	17.80	30.20
June 20 . .	40	2,018,000	14,800	5,772		55.60	2.50	1.20	3.20	37.30	12.90	26.10	39.00
June 21 . .	..	2,800,000	18,000	7,560		60.10	1.60	2.20	5.10	30.87	14.80	27.30	42.10
June 22 . .	41	2,280,000	11,600										
June 23 . .	45	2,180,000	12,000	3,345		61.50	3.54	1.60	3.50	30.00	8.33	19.55	27.88
June 24 . .	45	2,264,000	14,000	2,261		70.90	1.60	1.30	4.00	22.20	5.45	10.70	16.15
June 26 . .	45	.....	11,600	2,784		65.70	1.60	0.60	6.70	25.30	7.00	17.00	24.00
June 29 . .	46	2,300,000	11,600	1,032		67.50	2.00	1.00	3.20	26.30	3.80	5.10	8.90
July 2 . .	48	2,600,000	11,200										
July 6 . .	50	2,964,000	11,300	247		62.00	3.00	....	6.50	28.50	2.50	2.00	4.50
July 9 . .	46	2,890,000	5,500										
Nov. 28 . .	..	.....	.....	.....		64.50	4.50	1.50	3.00	26.00	0.50	1.00	1.50
1910													
Feb. 13 . .	..	.....	.....	.....		74.20	5.80	1.00	4.50	14.50	0.30	1.30	1.60

ingly variable in form. The majority of them showed a primitive form of nucleus with a definite chromatin network, and frequently more than one nucleolus. They answer very closely to the cells of bone marrow, or lymphoid cells, which, according to many, are the mother cells alike of the red and most of the white cells. These cells not infrequently showed mitotic figures. The other nucleated red cells showed a uniformly intensely blue staining nucleus or several nuclei, up to seven, an atypical budding appearing in some cases. Free nuclei of this description were frequently noted in the smear, some just becoming detached from the cell body. These free nuclei made the differentiation of lymphocytes a difficult matter. The majority of the nucleated red cells were megaloblasts, though normoblasts and some microblasts were present.

The smears were made on slides, stained with Wright's usual technique, and were counted under a Zeiss $\frac{1}{12}$ oil immersion lens. The cells were counted by the same Thoma-Zeiss hemocytometer throughout. The hemoglobin was estimated by two separate readings with the Dare hemoglobinometer. Smears made by the patient after he had left the hospital show more regularity in size and shape of the red cells, but there are still many nucleated forms. The color index, as mentioned, was always 1 or above 1.

During his stay in the hospital the patient improved greatly in general health; his jaundice disappeared and the spleen became rather smaller. In February last he wrote that he thinks his spleen is down to *its* usual size, and that he felt as well as he ever did in his life. This letter was accompanied by the last smear in the table, which still shows the great abnormality of the blood.

Remarks. The blood picture in this case by itself would suggest a diagnosis of pernicious anemia, the marked number of nucleated red cells and especially the great proportion of megaloblasts making it probable that we had to deal with the plastic form of this disease. The splenomegaly, although being unusual in pernicious anemia, would by no means exclude such a diagnosis, as cases are on record where the spleen has been quite as large as in this case, in which the disease was undoubtedly of the pernicious type. Osler[1] records such a case, which was at first taken to be one of splenic anemia,

[1] Transactions of the Association of American Physicians, 1902.

but subsequently came to *postmortem* and proved to be one of pernicious anemia. According to I. P. Lyon,[1] in something like 1 per cent. of all cases of pernicious anemia the spleen reaches to the umbilicus. Assuming for the moment that the case be one of pernicious anemia, then it presents several most unusual features. In the first place, the disease commenced at the age of eight years, if not sooner, which is very unusual. Again, it has lasted for at least twenty years, and the patient is still in fairly good health, and yet the longest recorded durations, apart from six cases of apparent recovery, only lasted between fourteen and fifteen years.[2] Further, according to the patient's history, he was so well between the ages of fourteen and twenty-eight that he was never laid up nor required medical advice—that is, he seems to have had a remission of fourteen years—and yet the longest recorded remission from prostrating symptoms on record is six years, according to Cabot.[3]

As regards splenic anemia, the enormous size of the spleen, with the marked anemia and normal differential white blood count, would, and did, suggest such a diagnosis, but the very profoundness of the anemia would be against such a conclusion; and, further, the fact that the anemia was always of the pernicious type, with a high color index, would seem to exclude this diagnosis.

Other forms of splenomegaly with anemia, such as congenital syphilis, tumor, malaria, and even the possibility of filaria, were all carefully weighed and excluded.

The case would appear to be either one of pernicious anemia of an exceptionally prolonged type, commencing at an exceptionally early age, and associated with an exceptionally enlarged spleen, or else one of splenic anemia, with a quite atypical blood picture.

The patient has left Canada for the United States, and we hope that his condition may be followed out by whomever he may consult.

[1] Osler's Modern Medicine, iv, 765.
[2] R. C. Cabot, Osler's Modern Medicine, iv, 635.
[3] Osler's Modern Medicine, iv, 633.

A STUDY OF EXPERIMENTAL CONDITIONS OF LOW BLOOD PRESSURE OF NON-TRAUMATIC ORIGIN.[1]

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The study of experimental conditions of low blood pressure has been limited, for the most part, to conditions of shock due to traumatism, thermic influences, or exposure, and aside from pharmacological investigations of the mode of action of certain substances, as arsenic, but few attempts to study, experimentally, low blood pressure due to toxic agents, have been made. The study of the latter should, therefore, be of interest not only to the internist, in that it may offer an explanation of conditions of collapse or shock occurring in medical as contrasted with surgical practice, but also of general importance, in that it supplements the experimental work of Crile[2] and others on surgical shock. Such a study has suggested by the observations of Biedl and Kraus,[3] which we[4] have confirmed, that anaphylactic shock in the dog is characterized by a low blood pressure resembling in many ways that of surgical shock. This condition, unaccompanied by mechanical injury or hemorrhage, but due to the action of horse serum on an animal in every way normal except that it had been sensitized to such serum, appeared to us to be analogous to

[1] Aided by a grant from the Rockefeller Institute for Medical Research.

[2] An Experimental Research into Surgical Shock, 1899; Blood Pressure in Surgery, 1903; Hemorrhage and Transfusion, 1909.

[3] Experimentelle Studien über Anaphylaxie, Wiener klin. Wochenschr., 1909, xxii, 363.

[4] Anaphylactic "Shock" in the Dog, Proc. Soc. Exp. Biol. and Med. 1909, vii, 30.

those conditions of suddenly developing low pressure occurring in medical as contrasted with surgical practice which are usually associated with a general intoxication. The close analogy between the blood pressure changes of anaphylactic "shock" and "peptone" intoxication led us to utilize the latter also in our studies.

The main object has been to study the treatment of low blood pressure, but in order to interpret properly the effects of treatment it was necessary first to determine the mechanism by which the low pressure was brought about and the effect of the alteration in pressure upon the general distribution of the blood. That portion of our study which deals with the mechanism of anaphylactic shock has been presented elsewhere.[1] The details of the mechanism of peptone intoxication only will be presented here, but as the mechanism of anaphylactic shock is analogous to that of the peptone effect, the descriptions of the latter illustrate also the former.

The change in the distribution of the blood was first studied. All animals were under full ether anesthesia. The pressure was taken from the left femoral artery with a mercury manometer; the peptone solution was injected at body temperature, and slowly, into the right femoral vein. The changes in blood distribution have been determined by oncometric studies of the spleen, kidney, and intestine, by a cannula introduced into the right common iliac vein and projecting into the inferior vena cava, by plethysmographic study of a forelimb, and by a metal cylinder penetrating the cranial cavity. Each of these pieces of apparatus was connected by rubber tubing with bellows recorders allowing simultaneous records on a revolving drum. It was thus possible in a single experiment to obtain simultaneously, as was frequently done, records of the circulatory variations in the femoral artery, the iliac vein, the kidney, the spleen, and the intestine, with also a record of the respiration, or any combination of these with a record of variations in the volume of a limb or in intracranial pressure. The temperature of the animals was maintained by a hot water coil encircling the greater part of the trunk. A record of temperature was obtained by a thermometer in the rectum. Peptone (Witte's) was injected intravenously, in the

[1] R. M. Pearce and A. B. Eisenbrey, The Physiology of Anaphylactic Shock in the Dog, Jour. Infect. Diseases, 1910, vii, 565.

strength of 10 per cent. in 0.85 per cent. salt solution. The solution was allowed to run into the vein slowly from a burette until a sharp fall in pressure occurred. The amount necessary varied considerably, but it usually required 0.2 to 0.4 gram per kilo to cause a fall in pressure lasting five minutes or more without upward tendency. This phase of our investigation includes ten observations.

It was found that "peptone" intoxication and anaphylactic "shock" are characterized by changes in the circulation which are closely analogous, except that in anaphylaxis the onset is more abrupt and the resulting condition more prolonged. In both a fall in blood pressure equal to 50 to 70 mm. Hg occurs immediately after injection. This is independent of initial changes in heart action, though during the continuance of the effect the pulse pressure is low, the result, apparently, of the small volume of blood passing through the heart. Respiratory disturbances, except in so far as they are secondary to the medullary anemia consequent upon the low general pressure, are absent.

Oncometric studies show a decrease in the volume of kidney, intestine, and spleen simultaneous with the fall in arterial pressure. Of these three organs, the decrease is, as a rule, most marked in the kidney and least in the intestine. A very slight initial decrease in brain volume has been found, as well as a slight diminution in the volume of an extremity. This decreased peripheral circulation is accompanied by an accumulation of blood in the large veins of the abdomen. This has been determined by inspection of the liver and large veins and by the observation that a cannula introduced into the inferior vena cava and connected with a water manometer shows a moderate increase of pressure equal to 6 to 10 mm. water, at the time of fall in arterial pressure, with an almost immediate return to normal level as the blood becomes evenly distributed throughout the large venous trunks.

It is evident, therefore, that the important feature of the condition of low pressure here described is a loss of tone of the vessels of the splanchnic area, resulting in extreme congestion of the large venous trunks. From this condition the animal does not quickly recover; and, as will be shown later, it is not readily influenced by circulatory stimulants. It is essentially the condition frequently characterized

as a "bleeding into the veins of the abdomen," and in many respects is analogous to the circulatory disturbance of surgical shock.

Our results with peptone differ somewhat from those of Thompson,[1] in that he found, by oncometric studies, a secondary rise in intestine volume. He lays much stress upon the influence of gravity, the secondary rise in intestine volume being most in evidence when the animal is placed on its side and the level of the oncometer lowered. This apparent mechanical error we have avoided by placing the intestinal and other oncometers in as nearly as possible the normal position of the organ under observation. The uniformity of our results leads us to believe that they are not affected by mechanical influences. This view is strengthened by the fact that the organ volume closely followed the general blood pressure, and transient changes in the latter, brought about in various ways, were always accompanied by changes in organ volume. Also, it may be stated that, by direct inspection during the stage of low pressure, the intestine showed no evidence of congestion except in the veins; the pallor of the tissue under such circumstances was striking.

The mechanism of the "peptone" reaction has been studied extensively. At present we are not especially concerned with the question of the nature of the substance in preparations of peptone which causes the effect on blood pressure.[2] It may be sufficient to state that the older view, based largely on the experiments of Pick and Spiro,[3] that the physiological effects were due not to the contained proteoses, but to impurities, has been rendered untenable by Underhill's results with purified products; also, that the contradictory results depend largely on the animal used; thus, the dog is found most susceptible, the cat less so, and the rabbit extremely resistant.

Concerning the physiological mechanism of the circulatory changes, we have no definite experiments previous to those of Thompson, though Pollitzer had described the blood pressure

[1] Contributions to the Physiological Effects of Peptone when Injected into the Circulation, Jour. of Physiol., 1896, xx, 455; 1899, xxiv, 374, 396; 1899, xxv, 1; 1900, xxv, 179.

[2] A summary of the literature to 1903 may be found in the excellent account by F. P. Underhill, New Experiments on the Physiological Action of the Proteoses, Amer. Jour. of Physiol., 1903, ix, 345.

[3] Ueber gerinuungshemmende Agentien im Orangismus höherer Wirhelthiere, Zeitschr. f. physiol. Chemie, 1900–01, xxxi, 237.

changes as due to a vasomotor paralysis affecting chiefly, if not wholly, the splanchnic region; and Grosjean, also, had ascribed to the vasodilatation the chief role, but believed it to be the result of a central disturbance. As the result of an extended series of experiments, Thompson concludes that the action of peptone is a direct or peripheral effect on the bloodvessels independent of the vasomotor centre. This effect, he thinks, is in all probability a depression of irritability limited to the nervous segment of the neuromuscular apparatus. His experiments include: (1) Division of the spinal cord and vagi; (2) excitation of the peripheral end of the cord; and (3) excitation of the divided splanchnic, the cord also being divided. Under all these conditions "peptone" caused a fall in pressure. Also, it was observed in the splanchnic excitation experiments that at the period of lowest blood pressure splanchnic stimulation gave, for a short period of time, no response.

Our study by physiological methods of the mechanism of changes in pressure due to "peptone" and that associated with anaphylactic shock, includes experiments in which the spinal cord, vagi, and cervical sympathetic and splanchnic nerves have been divided. The fall in pressure after peptone injection, as shown in nine experiments, is not influenced by any or all of these procedures; nor do such operative procedures have any effect in preventing the low pressure of anaphylaxis.

In order to eliminate completely any possible central factors in the production of peptone intoxication and anaphylactic shock, decapitated animals were used in addition to those having the cord, vagi, and cervical sympathetic nerves severed. Decapitation may be performed with a comparatively negligible amount of hemorrhage by clamping the common carotid arteries and the internal and external jugular veins simultaneously low in the neck, having first ligated the vertebral arteries at the point where they enter their canals in the transverse processes of the cervical vertebræ. After decapitation it was found that the blood pressure falls to a point averaging one-half of its original level and is maintained there for a period covering the usual length of the experiment, if care is exercised to keep the artificial respiration uniform and to maintain the body heat. With the loss of vagus influence, the heart rate is

quickened, the pulse pressure lowered, and the respiratory waves become well marked. Under such circumstances, however, both peptone and the toxic dose of horse serum cause a fall of blood pressure to the level occurring from similar doses in intact animals. The onset of the fall is less abrupt, the low level is reached more slowly, and the tendency to spontaneous recovery is markedly decreased.

When, in addition to decapitation, the cord is destroyed, there is a further fall in blood pressure to a point so low that the heart suffers from lack of blood, and death rapidly ensues from failure of the circulation. If, however, this extreme fall and low blood pressure level is combated, the cardiac anemia prevented, and a circulation sufficient for manometric record is established by increasing the blood volume by transfusion, it is found that the peptone and anaphylactic reactions may still be obtained. As a result of the extreme peripheral relaxation thus produced, a condition in which the vessels are practically a system of non-contractile tubes, cardiac anemia supervenes, and death quickly ensues. This demonstrates conclusively that the peptone and anaphylactic reactions may be produced independently of the medullary and spinal centres, by an influence on a vasomotor mechanism located either in the ganglia of the splanchnic area or at the neuromuscular junction in the vessel walls. The experiments in which the splanchnic nerves and ganglia were destroyed point to the neuromuscular junction as the seat of this action.

While these experiments on animals with the spinal cord destroyed after decapitation have shown that the usual effect on the blood pressure may be produced without central action, such experiments do not exclude the possibility that the central vasomotor mechanism may play some part in the symptom complex presented by intact animals. With the object of ascertaining the nature and extent of a possible central action without the complication of the known peripheral effects, we were obliged to devise a means by which the solutions used might be introduced into the cerebral circulation, but not reach the circulation of the body. A preliminary operation is performed, the details of which are described elsewhere,[1] whereby

[1] A. B. Eisenbrey, A Method of Isolating the Cerebro-medullary Circulation, Proc. Soc. Exper. Biol. and Med., 1901, vii.

vascular communication between the heart and the head and neck is obliterated and the circulation in the head and neck maintained independently by transfusion from a normal animal. Following a short period of irregularity due to the temporary changes in the cerebral circulation incidental to the technique of isolation, the general blood pressure of the recipient is maintained at a normal level, and solutions may be introduced into the cerebral or into the peripheral circulations exclusively, without any of the injected material reaching the other circulation. Under such circumstances the venous outflow from the cerebral circulation took place through an incision in the left external jugular vein, so that, following the injections, the brain receives normal blood only.

When peptone is injected into the cerebral circulation alone through the carotid anastomosis, a lowering of the general blood pressure occurs, but the depression is less marked and of shorter duration than when the body alone or the entire circulation is involved. Thus, to quote one experiment, the fall in pressure after intracerebral injection was only 30 mm. Hg, whereas after an injection into the femoral vein, two minutes later, it was 72 mm. to the level usually obtained in the intact animal.

When the injection is made into the circulation of the trunk alone, or after recovery from the effects of the cerebral injection, it is found that the fall in pressure is more abrupt in its onset than that due to intracerebral injection, and also that the low level is maintained for a longer time. The recovery, however, occurs more quickly than in the intact animal, and is apparently due to the strong constrictor impulses coming from the active medullary centres.

Similar results were obtained when horse serum was injected into the cerebral circulation and then into the circulation of the trunk of a sensitized dog. After recovery from the slight temporary depression following the cerebral injection, the blood pressure shows the typical profound depression of anaphylactic shock when the horse serum is injected into the saphenous vein. This is added evidence that the peripheral mechanism plays the essential part in the condition of anaphylactic shock.

We have, therefore, felt justified in concluding that in both peptone intoxication and anaphylaxis the action is wholly, or in largest

degree, peripheral, either on the nerve endings or on the musculature of the vessels. A number of pharmacological experiments have been made to still further localize the action. These are based on the experiments of Dixon,[1] and Brodie and Dixon[2] with apocodeine. This substance in very large doses paralyzes vasomotor nerve endings; and "when its action is complete, pilocarpine, physostigmine, and adrenalin have no effect on the bloodvessels or blood pressure, while barium and digitalis will still constrict the bloodvessels and raise blood pressure. The first three drugs, it is therefore assumed, act on nerve endings, and the latter two directly on muscle."

As the low pressure of anaphylaxis, both in its degree and in permanence, resembles closely that due to apocodeine, and as Thompson ascribes the peptone action to an effect on the nerve endings, we have tested the effect of adrenalin and barium in these two conditions. The results are not conclusive. While barium causes an increase in pressure, adrenalin does likewise; in the latter, however, the rise is but slight and never equal, even if percentile values are considered, to the normal adrenalin reaction.[3] Assuming, therefore, that adrenalin acts through the nerve endings, it is evident that in peptone intoxication and anaphylactic shock these structures are not completely paralyzed. Their activity, however, is greatly diminished, not only as shown by the slight adrenalin action, but also by the fact that splanchnic stimulation causes a smaller rise in pressure than in the normal animal. The muscle, on the other hand, is still very active. This is shown not only by the barium effect, but also by the effect of nitroglycerin, which, according to Dixon and Brodie, acts only on the muscle, and in the two conditions here described causes a further fall in pressure. Furthermore, if a sensitized dog under the influence of apocodeine receives an injec-

[1] The Paralysis of Nerve Cells and Nerve Endings, with Special Reference to the Alkaloid Apocodeine, Jour. of Physiol., 1903, xxx, 97.

[2] Contributions to the Physiology of the Lungs, Part II, on the Innervation of the Pulmonary Bloodvessels; and Some Observations on the Action of Suprarenal Extract, Jour. of Physiol., 1904, xxx, 476.

[3] If adrenalin and peptone are given together, the rise due to the former occurs immediately, but it is cut short by the peptone effect, which continues as usual. This has previously been shown by Hamburger. (The Action of Intravenous Injection of Glandular Extracts and Other Substances on the Blood Pressure, Amer. Jour. of Physiol., 1904, xi, 282.)

tion of serum, the typical reactions of anaphylactic shocks are not obtained. In fact, the blood pressure is raised a few millimeters by the mechanical effect of the injection, and remains so for a period of about one minute, gradually returning to a point slightly below the original level after two minutes. The typical reactions to barium chloride and nitroglycerin are obtained, but dog's urine, which, as we have shown elsewhere,[1] acts on the nerve endings, exerts no depressor effect, and adrenalin but slight pressor effect. It is therefore evident that in these conditions of low pressure the injury to the peripheral vasomotor mechanism is one involving the nerve endings rather than the muscle; the function of the nerve endings, however, is not completely in abeyance.[2]

Treatment. From the foregoing discussion of the causation of low blood pressure in "peptone" intoxication and anaphylactic "shock," it is evident that our therapeutic experiments have for their object the amelioration of a circulatory condition due to an action on the peripheral vasomotor apparatus and characterized by an excessive accumulation of blood in the large venous trunks of the abdomen. There is, however, this difference in the character of the low pressure due to "peptone" and that due to anaphylaxis, which must be clearly recognized in considering the results of therapeusis. Although the anaphylactic condition may be of short duration, it is usually characterized by a low circulatory condition, which frequently persists for long periods of time without change, and is closely analogous to the condition of shock, as generally known. All changes due to treatment under such circumstances are, therefore, to be ascribed directly to the action of the agent employed, with but slight tendency to immediate spontaneous recuperation on the part of the animal. On the other hand, the low blood pressure of peptone intoxication is maintained in the average intoxications for only five to six minutes, with, after that time, a gradual tendency to improvement. It resembles a condition of collapse rather than shock. Under such circumstances all treatment after

[1] See R. M. Pearce and A. B. Eisenbrey, The Mechanism of the Depressor Action of Dog's Urine, with Some Observations on the Antagonistic Action of Adrenalin, Amer. Jour. of Phys., 1910, xxvi, 26.

[2] The experiments described here were carried out on both types of low pressure and also on animals with the peptone effect added to that of anaphylaxis. The results were the same.

the first few minutes must be considered as aiding the natural recuperative power of the temporarily embarrassed vasomotor system.

Treatment by Transfusion. The condition of the general circulation following an increase in blood volume by transfusion, after some of the experimental procedures directed against the different divisions of the vasomotor system, serves to illustrate the importance of the role played by these separate divisions in the process of recovery. When a dog is decapitated and transfused, the blood pressure rises rapidly in proportion to the duration of transfusion, and is well maintained. When, however, in addition to decapitation, the spinal cord is mechanically destroyed, transfusion causes a delayed and inadequate rise, that is poorly sustained. With the loss of tonic constrictor impulses from the spinal centres, a passive dilatation of the vessels occurs, and the small, slow rise in pressure obtained with even a copious transfusion does not appear until the vessels are practically distended to their full limit, and is, presumably, purely a mechanical feature. Before a level is reached which is comparable to the level obtained by a similar transfusion in a decapitated animal, the distention and loss of elasticity of the vessels is so great that the heart which is receiving an insufficient blood supply is unable to increase the arterial pressure sufficiently to relieve the venous congestion.

The condition of the circulation in anaphylactic shock[1] is, in a way, analogous to that of an animal with spinal cord and medullary centres destroyed. Both centres exert little or no influence on the peripheral mechanism owing to the blocking at the neuro-muscular junction, and the regulatory function of the medullary centres is further influenced by the local anemia consequent upon general low pressure. Consequently, venous transfusion increases the dilatation of the peripheral circulation and causes an increased congestion of the splanchnic area, without materially augmenting the amount of blood going to the heart and medulla. If we compare the circulatory condition of anaphylactic shock with that of hemorrhage, we find in both a common condition—anemia of the medullary centres—but

[1] The peptone intoxication on account of the tendency to spontaneous recovery, although analogous, is not strictly comparable on account of the tendency to gradual spontaneous recovery.

widely different conditions in the peripheral mechanism. In anaphylactic shock the latter is out of function, while in hemorrhage its regulatory power is intact, and thus is maintained a fairly efficient circulation, supplying the heart and medulla, and venous transfusion under such circumstances causes a rapid return to normal. In anaphylactic low pressure, on the other hand, such transfusion increases the splanchnic congestion without aiding the heart or the medulla. It is evident, therefore, that the two conditions to be combated are (1) the congestion of the splanchnic area, and (2) the anemia of the heart and medulla. As preliminary experiments showed that drugs have little or no power to overcome both conditions, we resorted to arterial transfusion to relieve the second, and in some experiments have bled simultaneously from the central end of the femoral veins, to reduce the splanchnic congestion.

This combination has been most successful. Bleeding from the femoral vein removes from the great veins of the abdomen a large amount of blood containing accumulated toxic products and also allows the relatively fresh blood of arterial transfusion to come in contact with the splanchnic vessels, thus presumably hastening the recovery of the peripheral vasomotor mechanism. At the same time the transfusion (by carotid anastomosis) brings a large volume of fresh arterial blood directly to the capillaries of the medulla and the heart,[1] and hastens their recovery before materially adding to the volume of the blood in the large venous trunks of the splanchnic area. This combination of venous bleeding and arterial transfusion is efficacious in both peptone intoxication and anaphylactic shock, and readily brings about a condition of stabile equilibrium. On the other hand, arterial transfusion, alone, of moderate degree, has been sufficient to bring about a restoration of pressure with maintenance at the original level, but the danger of overtransfusion and cardiac breakdown is greater.

These observations demonstrate conclusively the importance of the part played by the medullary centres in recovery from conditions of low blood pressure.[2] This has been well illustrated in the work

[1] Anastomosis of a carotid of the donor to the central end of a carotid of the recipient allows, on account of the low pressure of the latter, the direct passage of blood not only to the brain of the recipient through the other carotid, but also to the coronary arteries, thus directly supplying the capillaries of the heart muscle.

[2] See G. Crile and D. H. Dolley, On the Effect of Complete Anemia of the Central Nervous System in Dogs Resuscitated after Relative Death, Jour. Exper. Med., 1908, x, 782.

with an isolated cerebral circulation, when, with these centres unaffected by the depressing agent and having a constant independent blood supply, the duration of low blood pressure following the intravenous injection into the trunk of peptone or the anaphylactic dose of horse serum, was markedly decreased, and the recovery more rapid than is the case in the intact animal.

These results, successful as they are in experimental procedure, can hardly be recommended as a basis for similar therapeutic measures in treating low blood pressure in man. They do, however, offer a very satisfactory basis for the experimental study of the influence of drugs and other remedial agents.

Treatment by Drugs. Since in peptone intoxication the blood pressure tends to rise spontaneously after ten to fifteen minutes, even when large doses are given, the attempts to overcome the effects of peptone by therapeutic measures have been confined to the period when spontaneous recovery was not to be expected. We have assumed that, if within a period of five minutes after the production of peptone intoxication the blood pressure could be raised and sustained at the normal level throughout the usual period of peptone action, a satisfactory line of treatment for this and analogous clinical conditions would be indicated.

With this end in view we have employed normal saline solution, adrenalin, caffeine, digitoxin, and strophanthin. These were administered through a cannula in the saphenous vein, with due regard to the temperature of the solutions and the rate of injection.

It was found that saline solution has its usual effect, proportionate to the amount injected, of mechanically raising the pressure, which, however, is not well sustained, owing to the rapid passage of the fluid into the tissues. The administration of cardiac stimulants simultaneously, while causing increased heart action in the usual degree and a still further rise in pressure, does not suffice to offset the loss of the mechanical effect of the saline.

Adrenalin in therapeutic doses in normal saline solution causes the most satisfactory rise in the blood pressure, and with it a heart action quite comparable to that obtained before the administration of the peptone. This improvement, however, is limited by the duration of the adrenalin action. Again, the simultaneous admin-

istration of cardiac stimulants causes a further rise and a more prolonged effect, but as the constrictor effect of the adrenalin wears off, the blood pressure again returns to a low level. During the maximal peptone action the rise of blood pressure following adrenalin administration is small and transient, even on a percentile basis. But if such administration is made late in the peptone action, when the vasomotor endings are recovering, and the medullary centres are likewise improving, even though the pressure is still low, the rise is proportionately greater, and subsequently the general pressure is sustained at a normal level.

The response to cardiac stimulation in so far as the heart itself is concerned is quite as active and as well within the normal limits as before the administration of peptone, but owing to the peripheral dilatation and the diminished volume of blood reaching the heart, the slight improvement in the general blood pressure which ensues is quite transient. The heart shows the effect of overaction, due to insufficient blood supply, its contractions weaken, and the blood pressure quickly returns to or below the former level. If, however, as with adrenalin, such treatment is instituted toward the end of the peptone action, the recovery is much hastened, and the heightened blood pressure due to the increased heart action is well sustained.

While we are unable to directly neutralize the effect of the peptone intoxication, or to activate the peripheral vasomotor mechanism, and are convinced of the futility of attempting to combat the condition by cardiac stimulants alone, the results obtained by the employment of a slow continuous injection of adrenalin in salt solution (1 to 40,000), administered intravenously, with the addition of a pure cardiac stimulant, such as digitoxin, thus promoting the determination of blood to the right heart and an increased circulation in the brain, lead to the conclusion that a similar line of treatment is indicated in those clinical emergencies that present an analogous circulatory condition. Such treatment is not, however, specific or curative, except in so far as it serves to tide over successfully the critical period until the effects of the toxic agent have worn off and the normal functions of the vasomotor mechanism are resumed. This has been satisfactorily demonstrated in the more prolonged condition of anaphylactic shock, in which, as during the early stage

of peptone intoxication, adrenalin has a minimal effect, and in which, likewise, cardiac stimulants alone are unable to overcome the effects of the paralysis of the vasomotor nerve endings. On the other hand, a combination of the peripheral constrictor effect of slow continuous injection of adrenalin, of salt solution, and of an active cardiac stimulant brings the circulation within the normal limits long before spontaneous recovery could be expected to occur, and maintains it at this level.

SUMMARY. Anaphylactic shock and peptone intoxication are characterized by conditions of low blood pressure very similar to those seen in shock and collapse, and, as they are produced without trauma or other factors usually concerned in the etiology of surgical shock, are of interest in the study of conditions of shock occurring in medical as contrasted with surgical practice.

Both conditions are characterized by a fall in blood pressure to a level of 20 to 30 mm. Hg, which is prolonged in anaphylactic shock, but tends to relatively rapid recovery in peptone intoxication. In both conditions there is an extreme congestion of the large venous trunks of the splanchnic area, with a coincident medullary anemia. The respiration is not altered, except in so far as it is affected by the anemia of the medullary centres; the heart shows no initial changes, the low pulse pressure being due apparently to the small amount of blood passing through it.

Physiological studies, having for their object the determination of the mechanism by which the low pressure is caused, demonstrate that the condition is essentially a peripheral vasomotor paralysis. Pharmacological studies indicate that the effect is on the nerve endings rather than the muscle.

With independent cerebral transfusion, the recovery from low pressure is more rapid than in the intact animal. This is true also when an animal is transfused by carotid anastomosis, and recovery is especially satisfactory when the transfusion is accompanied by simultaneous bleeding from the femoral vein.

The indications for treatment, therefore, appear to be (1) relief of splanchnic congestion, and (2) increase of volume of blood to the heart and medulla. Cardiac stimulants alone, or salt solution or adrenalin alone, cannot bring about a permanent improvement. A

combination, however, of the slow injection of adrenalin in salt solution (1 to 40,000) intravenously, with the addition of a pure cardiac stimulant, as digitoxin, lead to relatively rapid and permanent improvement, by promoting a determination of the blood to the right heart and increasing the circulation in the brain.

The results of the experimental treatment of this condition, which, for want of a better name, may be called toxic shock, are not essentially different from those in traumatic shock.

THE EFFECT OF PERMANENT CONSTRICTION OF THE SPLANCHNIC ARTERIES AND THE ASSOCIATION OF CARDIAC HYPERTROPHY WITH ARTERIOSCLEROSIS.

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The importance of arteriosclerosis as a cause of cardiac hypertrophy is a problem which for many years has attracted the attention of both pathologists and clinicians, but even after the most extensive studies upon the subject, one must admit that the question is as yet far from settled. The great obstacle to the elucidation of this problem has been the difficulty in obtaining an exact method for study. So far, most of our conclusions have been drawn from the examination of autopsy material, and it is well known how many and what complicated factors confront one under these circumstances. Diseases of the bloodvessels are so frequently associated with other conditions, such as chronic nephritis, which of themselves may lead to hypertrophy, that it is with the greatest difficulty that one can make accurate deductions concerning the direct influence of arteriosclerosis.

It seems, however, to have been satisfactorily shown that sclerosis of the peripheral vessels is not necessarily accompanied either by an increase in blood pressure or hypertrophy of the heart. On the other hand, it has been quite generally assumed, since the publication of the work of Hasenfeld[1] and Hirsch,[2] that arteriosclerosis of the thoracic and abdominal aorta, and especially narrowing of the lumina of the splanchnic arteries, may be a potent factor in the causation of cardiac hypertrophy. Though Marchand states that he could not from his own experience confirm this view, it may

nevertheless, be said that the careful observations, especially of Hasenfeld and Hirsch, have done much to substantiate this claim.

But the question has not been put to experimental test. It was, therefore, the object of the present study to attempt first to reproduce as nearly as possible, by experimental methods, a narrowing by arteriosclerotic processes of the lumen of the celiac axis and superior mesenteric artery; and secondly, to study subsequently the effect of this operation upon the blood pressure and heart. In some previous experiments it was found that constriction of either the superior mesenteric artery or celiac axis in dogs caused an immediate rise in blood pressure of from 8 to 22 mm. Hg, with an average of 14 mm. Hg, while constriction of the two arteries at the same time about doubled this rise. The rise in general blood pressure was, moreover, not fleeting, but persisted in some experiments for at least an hour.

It was thought, therefore, quite possible that permanent constriction of these arteries might be accompanied by a continuous increase in blood pressure with the development of cardiac hypertrophy.

For the following experiments dogs were used exclusively. The animals were etherized and the abdomen opened to the right or left of the midline, sometimes directly in the midline. The superior mesenteric artery and celiac axis were dissected free from the dense plexus of nerves which surrounds them as they branch from the aorta, and by means of the ingeniously devised instrument described by Halsted[3] (the instruments which we used were kindly lent by Dr. Halsted), aluminum bands, 3 to 4 mm. in width, were rolled about the vessels. These bands were then tightened about the arteries with the finger until the pulsation in the distal side was greatly reduced in force, or almost obliterated. The wound was then closed.

At intervals covering months after the operation the blood pressure of the dogs was studied. For this purpose the cuff devised by Janeway[4] was employed, attached to a Stanton manometer. Owing to the fact that the proper apparatus was at first not obtained, and to the fact that some time was required to develop our technique, the pressure of the dogs during the early experiments was not estimated before the operation. Later, however, estimations were made before the operation, often several times, as controls for the later readings.

Bands were thus placed either about the superior mesenteric artery alone or both the superior mesenteric artery and celiac axis of 16 dogs. Seven of these dogs died within a week of the operation—2 from pneumonia and 5 from infarction of the intestines following thrombosis of one or both of the constricted arteries. One dog died on the eleventh day of a phlegmon of the stomach, and one on the thirteenth day from pneumonia. Seven dogs have been studied over a period of from three to five months. In 4 dogs the superior mesenteric artery alone was constricted; in 5 dogs both vessels were surrounded by bands. The following is an abstract of the protocols of the last 9 dogs:

Dog 279.—Fox terrier type, male; weight, 24 pounds.

November 9. Operation; band placed about superior mesenteric artery; fair pulse in arteries of omentum. Dog recovered well; lost weight.

November 29. Weight, 23 pounds; thin, but eating well.

December 7. Weight, 23 pounds. Stools hard and black.

December 29. Weight, 22½ pounds.

January 12. Weight, 21½ pounds.

January 17. Systolic pressure, 130 to 118.

January 20. Weight, 23½ pounds.

January 31. Systolic pressure, 125 to 112.

February 3. Weight, 25 pounds.

April 15. Systolic pressure, 135 to 118.

April 22. Systolic pressure, 115 to 130.

Killed April 25, 1910. Band closely approximated about artery, but lumen patent, though tightly constricted. All the organs are normal.

Dog. 280.—Fox terrier type, male; weight, 18 pounds.

November 17. Aluminum band placed about superior mesenteric artery.

November 29. Dog thin; stitch abscess.

December 1. Weight, 17 pounds; eats well.

December 10. Weight, 18 pounds; in good condition.

January 12. Weight, 19 pounds.

January 17. Systolic pressure, 100 to 125.

February 3. Weight, 18½ pounds.

April. Dog lost.

Dog. 276.—Male; weight, 18 pounds.

October 26. Operation; band placed about superior mesenteric artery.

November 4. Dog not well; wound healed; languid.

November 8. During last few days stools dark brown and soft; losing weight.

Died November 8, pneumonia with purulent pleurisy, congestion of intestines and liver; the band is in place and shows tight constriction of vessel, which is patent.

Dog 282.—Black and tan, male.

November 22, 1909. Operation; aluminum band placed about superior mesenteric artery.

November 29. Doing well.

December 1. Weight, 22 pounds.

December 7. Weight, 20 pounds; stools seem normal.

December 15. Systolic pressure, 85; weight, 22 pounds.

January 12. In good condition; weight, 21 pounds.

January 14. Systolic pressure, 70 to 80.

January 26. Systolic pressure, 78 to 82.

February 3. Weight, 20½ pounds.

April 5. The dog has bad mange; systolic pressure, 85 to 100.

Killed April 16, 1910. The band is tightly placed about superior mesenteric artery and the vessel is completely converted into a fibrous cord.

Dog 283.—Small white fox terrier, male; weight, 13 pounds.

November 30, 1909. Operation; band placed about superior mesenteric artery.

December 7. Stools soft and dark; weight, 11 pounds; does not eat well.

December 15. Improving; weight, 10 pounds; stools soft and dark.

January 5. Weight, 12 pounds.

January 12. Weight, 14 pounds.

January 26. Systolic pressure, 90 to 95.

February 3. Weight, 15 pounds.

April 5, 1910. Systolic pressure, 85 to 100; dog in rather poor condition. Killed April 6, on account of mange. The superior mesenteric artery is converted into a fibrous cord and completely

occluded. The organs are normal. Berlin blue injected into the femoral artery reaches the entire small intestine before it colors the stomach.

Dog 288.—Brindle, male.

December 7, 1909. Operation; aluminum bands placed about superior mesenteric artery and celiac axis; marked thrill on distal side of bands.

December 8. Systolic pressure, 95 to 105.

December 10. Good condition; stools lost; weight, 28 pounds.

December 15. Weight, 27 pounds; systolic pressure, 120 to 125; there is diarrhea.

December 29. Systolic pressure, 85.

January 5. Weight, 27 pounds.

January 12. Weight, 26 pounds; condition good.

January 14. Systolic pressure, 95 to 102.

January 22. Stools again normal.

January 26. Systolic pressure, 95 to 100.

February 3. Weight, 27 pounds.

April 5. Dog is thin and has the mange; systolic pressure, 105 to 110.

Killed April 18, 1910. Both bands in place and both arteries patulous, though the lumina are constricted.

Dog 290.—Large black and white, male; weight, 36 pounds.

December 15. Systolic pressure, 115 to 120.

December 17. Systolic pressure, 113 to 120.

December 18. Systolic pressure, during operation, 107 to 115.

Operation; bands placed about superior mesenteric artery and celiac axis; immediately after bands in place, systolic pressure, 115 to 125.

December 20. Good condition; pressure cannot be obtained.

January 5. Weight, 32 pounds.

January 14. Systolic pressure, 128 to 132.

January 20. Weight, 34 pounds.

January 26. Systolic pressure, 128 to 132.

February 3. Weight, 35 pounds.

February 15. Systolic pressure, 128 to 130; soft brown stools.

Killed March 14, 1910. The celiac axis is completely converted into a fibrous cord; the superior mesenteric artery is surrounded by

the band; the lumen is narrowed to almost pinhole size, but patulous; the organs are normal.

Dog 293.—Brown, fairly large male; weight, 26 pounds.

January 10. Systolic pressure, 90 to 93.

January 11. Systolic pressure, 92 to 87.

Operation; bands placed quite tightly about superior mesenteric artery and celiac axis; scarcely any pulsation felt in distal part of artery.

January 12. In good condition; systolic pressure, 74 to 77.

January 17. Systolic pressure, 110 to 112.

January 20. Weight, 20 pounds.

January 21. Dog developed bloody stools and vomited blood. Died January 21, 1910. The stomach shows hemorrhagic phlegmon; the intestines are intensely congested; the bands surround the celiac axis and superior mesenteric artery and seemingly constrict the lumen, but do not occlude it.

Dog 294.—White pointer, large male; weight, 30 pounds.

January 10. Systolic pressure, 92 to 107.

January 17. Systolic pressure, 98 to 112.

January 18. Operation; bands put about celiac axis and superior mesenteric artery.

January 20. In good condition; weight, 30 pounds.

January 24. Systolic pressure, 111 to 124; wound not healing well.

January 31. Wound in much better condition; systolic pressure, 115 to 130; weight, 24½ pounds.

February 7. Systolic pressure, 90 to 100.

April 15. Systolic pressure, 120.

April 22. Systolic pressure, 120 to 110.

Killed April 27, 1910. The organs are normal, except for some congestion of the liver. The superior mesenteric artery and celiac axis are tightly surrounded by the bands, and the lumina are constricted to pinhole size, but patulous.

Immediately after the operation all the dogs rapidly lost weight, but in many instances this was soon regained. Digestive disturbances were frequent. A few dogs developed diarrhea, with soft dark stools; one dog died with extensive phlegmonous gastritis.

The effect upon the blood pressure may be seen in the following table.

TABLE I.—BLOOD PRESSURE.

No.	Operation.	Arteries constricted.	Dec. 8.	Dec. 15.	Dec. 17.	Dec. 18.	Dec. 29.	Jan. 10.	Jan. 11.	Jan. 14.	Jan. 17.	Jan. 18.	Jan. 24.	Jan. 26.	Jan. 31.	Feb. 7.	Feb. 15.	Feb. 16.	Feb. 21.	April 5.	April 15.	April 22.	Death.
279	Nov. 9	Sup. mesen.	..	..	123	..	..	..	..	..	..	..	..	..	114	..	..	..	..	..	124	121	April 25
280	Nov. 17	" "	..	..	..	..	..	..	..	..	113	..	..	..	..	..	..	..	..	..	..	..	Lost
282	Nov. 22	" "	..	..	..	..	..	..	..	76	..	..	..	81	..	..	..	..	..	97	†	..	April 16
283	Nov. 30	" "	..	..	..	..	..	..	..	..	..	..	..	91	..	..	..	..	..	90	†	..	April 6
288	Dec. 7	Sup. mesen. celiac axis	100	122	..	..	85	..	..	98	..	..	..	97	..	..	..	..	..	102	..	†	April 18
290	Dec. 18	" "	..	117	..	* 119	..	..	..	130	..	..	..	129	..	..	129	..	..	†	..	..	March 14
293	Jan. 11	" "	..	..	..	..	..	92	* 92	..	112	†	..	..	..	..	..	..	..	..	..	..	Jan. 21
294	Jan. 18	" "	..	..	..	..	..	102	105	..	..	*	117	..	124	95	..	..	..	..	120	115	April 27
295	Feb. 16	" "	..	..	..	..	..	..	..	..	116	..	102	..	119	..	98	*	102	†	..	..	Feb. 23

The numbers are the averages of 6 to 12 separate readings. The systolic pressure is computed from the moment that the pulse in the paw disappears.
* = Day of operation. † = Time of death.

It is evident that there is no definite change in the blood pressure following these experiments. In Dogs 290, 293, and 294 there is a slight rise, varying from 11 to 19 mm. Hg after the operation, but the elevation is not constant and is not sustained. In no instance did the blood pressure rise above a limit which is reached by normal dogs, as could be determined in control experiments. Except for the transient disturbances described, no ill effects upon the health of the dogs could be observed.

After periods varying from four to six months the dogs were killed and their hearts weighed by Müller's[5] method. The following table gives the results of this analysis:

TABLE II.

No.	Operation.	Duration of Experiment.	Condition at death.	Weight of dog in gms.	Weight of whole heart.	Prop.	Weight of ventricles.	Proportion.
298	Sup. mesen. celiac axis	1 day	Fair	13610	109.5	0.008	99.5	0.0073
297	" "	7 days	Fair	7460	64.0	0.00857	56.0	0.0075
295	" "	7 days	Fair	13560	122.5	0.009	111.0	0.00818
293	" "	11 days	Lost 6 pounds	8400	84.5	0.010	77.7	0.009
283	Sup. mesen.	4 mos. 7 days	Emaciated	5520	51.0	0.0092	44.1	0.00797
290	Sup. mesen. celiac axis	3 months	Fair	14500	117.5	0.0081	104.0	0.0071
279	Sup. mesen.	5 mos. 14 days	Good	11500	85.5	0.00743	75.5	0.00656
282	" "	4 mos. 24 days	Fair	9100	65.9	0.00724	59.5	0.00653
288	Sup. mesen. celiac axis	4 mos. 11 days	Fair	11640	82.5	0.00709	75.3	0.00647
294	" "	3 mos. 9 days	Good	11000	90.0	0.00818	79.7	0.00724

Twenty-eight normal dogs. Male.
The ratio of body weight to weight of whole heart varied from 0.0063 to 0.0089.
The ratio of body weight of ventricles varied from 0.0055 to 0.0078.

When we examine the ratios of the weights of the whole heart and of the ventricles to the body weight of these dogs, we see immediately that, except for three instances, they fall well within the normal limits. The ratio for the whole heart in the operative series varied between 0.00709 and 0.0086, and for the ventricles

between 0.00647 and 0.0075. In 28 normal dogs used as controls the figures for the whole heart varied between 0.0063 and 0.00898, and for the ventricles, between 0.0055 and 0.00782. Two of the 3 dogs of the operative series died seven and eleven days, respectively, after the operation, and the slight increase in the ratio is unquestionably due to the rapid loss in body weight following operation. The third dog which showed the high ratio was killed four months and seven days after operation. During the last week or ten days of life, however, he had lost weight very rapidly, which, again, may account for the comparatively high figure. In all the dogs the valves were carefully examined in order to exclude any accidental valvular lesions which might lead to hypertrophy.

Four dogs died within two weeks of the operation. In three of these, though there was no thrombosis of the arteries constricted, a marked congestion of the stomach, intestines, spleen, and liver was found. In 2 cases this may have been due in part to the acute infection of the lungs which was present, but in one dog this factor could be eliminated. In the fourth dog there was thrombosis of both vessels, but there was no actual infarction of the intestines or of the other viscera. From previous observations, and from the clinical symptoms which some of these dogs presented during the first week or two after operation (diarrhea, with soft, dark bowel movements), we are led to the conclusion that the first effect of diminishing the arterial blood supply to the intestines and liver, by narrowing the lumen of the superior mesenteric artery and celiac axis, is not an anemia, but a congestion of the organs supplied by these vessels.

After complete occlusion of these vessels hemorrhagic infarction develops. During this process the blood arrives in the intestines by way of the slight collateral anastomosis which the superior mesenteric artery makes with the inferior mesenteric. If, however, the occlusion of these vessels is not complete, there is still sufficient pressure in the distal portion of the arteries to prevent complete hemorrhagic necrosis of the intestines, but not enough to maintain a normal circulation. The result is, therefore, an immediate congestion in this region. But an efficient collateral circulation may be very soon established, for in Dog 297 the superior mesenteric artery was found completely thrombosed seven days after the operation, though there was no hemorrhagic necrosis of the intestines.

Autopsies upon the 7 dogs that were killed over periods of from three to five months after operation showed that in all cases the organs were normal, except, perhaps, for some congestion of the liver. In 2 dogs (279 and 288) the bands were found to constrict either the superior mesenteric artery or celiac axis to a considerable degree, though the lumina of both vessels were patent. In 2 dogs (282 and 283) the superior mesenteric artery was completely converted into a fibrous cord, and in 1 dog (290) the celiac axis was completely converted into a fibrous cord, while the lumen of the superior mesenteric artery, though patulous, was narrowed to a pinhole size. An injection of Berlin blue into the femoral artery of one of the dogs in which the superior mesenteric artery was completely thrombosed showed that a free anastomosis had been established between the branches of the inferior mesenteric and superior mesenteric artery. The injecting fluid was seen to fill the vessels of the colon in the region supplied by the inferior mesenteric artery, and to pass through into the vessels of the small intestines, coloring the loops of the intestines blue before the stomach and spleen were injected.

From these experiments we can conclude, therefore, that extreme narrowing of the mouths of the superior mesenteric artery and celiac axis in dogs is soon compensated for by a collateral circulation, so that gradual thrombosis of one or both vessels may take place without serious or obvious detriment to the health of the animal. Neither cardiac hypertrophy nor hypertension follows the narrowing of the mouths of these vessels in dogs.

Certain criticisms might be offered to such conclusions. It is possible that the time elapsing between the operation and the date of death was not sufficiently long to allow for a noticeable increase in the weight of the heart. Friedländer,[6] however, has found that in children and young adults hyperpertrophy may be noticeable four weeks after the onset of acute scarlatinal nephritis, and there is no reason to suppose that hypertrophy may not occur as rapidly in dogs. Seven of the dogs were watched at least twice this long, without the slightest evidence of hypertrophy. Again, it may be said that the condition of the life of these animals after operation was not conducive to hypertrophy, but they were kept under exactly the same

conditions as the control dogs, and if the operation itself had had any effect upon the general vascular system a comparison with the control dogs should have demonstrated this.

We may now ask whether it is justifiable to draw conclusions from these experiments as regards cardiac hypertrophy in man. To determine this point we have examined during the last three years with particular care the condition of the branches of the abdominal aorta at autopsy, and have compared the state of these vessels with the weight of the heart. The heart, however, has not been weighed by Müller's method, but the condition of the organ has been computed by the usual methods. During this time we have found 46 cases, tabulated below, in which either the heart showed hypertrophy or the mesenteric artery and celiac axis were narrowed, often to an extreme degree, by arteriosclerotic processes, pressure from aneurysms, or from newgrowths. Naturally, all cases in which there was a valvular lesion or disease of the pericardium have been excluded.

TABLE III.—Cardiac Hypertrophy (37 Cases).

Associated with sclerosis of abdominal aorta and narrowing of splanchnic arteries.	Chronic nephritis present, 10 Chronic nephritis absent, 2	12
Unassociated with sclerosis of abdominal aorta or narrowing of splanchnic arteries.	Chronic nephritis present, 20 Chronic nephritis absent, 5	25
	Total	37

Sclerosis of Abdominal Aorta and Narrowing of Splanchnic Arteries (21 Cases).

Cardiac hypertrophy.	Chronic nephritis present, 10 Chronic nephritis absent, 2	12
No cardiac hypertrophy.	Chronic nephritis present, 6 Chronic nephritis absent, 3	9
	Total	21

In this series there were 37 cases of definite cardiac hypertrophy; of these 37 cases, 12, or about 32 per cent., showed extensive sclerosis of the abdominal aorta with narrowing of the mouths of the splanchnic vessels, or definite stenosis of one or both of the arteries themselves.

On the other hand, 30, or 81.3 per cent., were associated with chronic nephritis. Now, of the 12 cases in which narrowing of the splanchnic vessels occurred in combination with cardiac hyper-

trophy, 10, or over 83.3 per cent., showed chronic nephritis, and in the 2 cases in which there was no nephritis the hypertrophy was of very slight grade. Finally, there were 9 cases in which narrowing of the superior mesenteric artery and celiac axis occurred in which there was no cardiac hypertrophy demonstrable by the methods employed. In 5 cases at least the lesion of the abdominal aorta and splanchnic vessels was of a most extreme grade. In one instance both vessels were almost occluded by pressure from a new-growth, in one instance a dissecting aneurysm of the celiac axis narrowed the lumen to a mere slit, and in three instances there was extreme sclerosis of the abdominal aorta, with much constriction of the superior mesenteric artery and celiac axis. Indeed, of the 21 cases in which the splanchnic vessels were narrowed, only 7 were associated with any degree of cardiac hypertrophy, and in all 7 cases a definite chronic nephritis co-existed.

Our experience at autopsy is therefore in accord with that of Marchand,[7] who could find no definite association between cardiac hypertrophy and sclerosis of the abdominal aorta or splanchnic vessels.

From these experiments and observations at autopsy, it would seem highly improbable that any anatomical lesion of the larger vessels, even in the splanchnic area, can produce a marked increase of blood pressure or give rise to hypertrophy of the heart. The gradual narrowing of the vessels which occurs in such a process, even when it is widespread, is soon compensated for by collateral anastomoses, so that the distribution of the volume of blood in the body is equalized.

That narrowing of the main splanchnic arteries may cause a rise of blood pressure in any other manner than by shunting off into the general circulation a certain proportion of the volume of blood flowing to the intestines is unlikely, from the results of previous experiments upon dogs; for it was found that the rise of blood pressure following immediately upon occlusion of the superior mesenteric artery and celiac axis was not due to a possible reflex arising from the anemic intestines and causing constriction of the arteries in other parts of the body. On the other hand, the excess of blood thrown into the general circulation by this procedure was not sufficiently

compensated for by a dilatation of the vessels of other organs, and the general blood pressure soon rose, owing to the rapid increase of blood in the general circulation which was not compensated for.

Mall[8] has explained the rise of pressure which follows constriction of the splanchnic arteries, and, indeed, the mesenteric veins as well, following stimulation of the splanchnic nerves upon the same basis. The results of sclerosis of the splanchnic arterioles may be quite different from that of narrowing of the main arteries, but the present investigation is, of course, not concerned with this problem. A study, however, of the condition of the finest branches of the mesenteric artery is now being made in connection with observations upon the blood pressure during life.

Conclusions. We conclude, therefore, that sudden occlusions of the superior mesenteric artery in dogs results in hemorrhagic infarction of the intestines. Permanent constriction of the superior mesenteric artery and celiac axis, as well as gradual occlusion of one or both of these vessels, may be present in dogs for at least five months without giving rise to a definite and constant elevation of blood pressure or to hypertrophy of the heart.

At autopsy no definite association can be found in man between sclerosis of the abdominal aorta and splanchnic vessels and cardiac hypertrophy.

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SOME REACTIONS OF THE VASOMOTOR CENTRE.

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A correct appreciation of the conditions of the circulation demands the analysis of the different mechanisms by which it may be affected under various conditions. Among these mechanisms the vasomotor centre holds a very important place, and its reactions have therefore been the subject of many investigations. The methods which are commonly used depend mainly upon the observation of the blood pressure or the volume of organs, or the vein flow. These serve admirably when the effects can be referred with certainty exclusively to the vasomotor centre; but their analysis is usually impossible when there may be simultaneous changes in the heart, in the total volume of blood, or in the peripheral vascular mechanism. Since such complications cannot often be excluded, *a priori*, our knowledge of the central vasomotor reactions is still very limited. What we know or think we know is beset with considerable uncertainty. Certainty can only be reached by the use of methods which eliminate the complicating factors; *i. e.*, by so adjusting conditions that the circulation through the observed vessels can be modified through the vasomotor centre, and in no other manner. This demands, of course, that the organ be separated from the systemic circulation, and subjected to artificial perfusion. If the vasomotor nerves are left connected with the centre, the desired conditions are attained. The state of the vessels

can be conveniently recorded by measuring the outflow of the perfusing fluid; a slowing of the flow corresponds to central vasoconstriction or stimulation; a quickening of the flow means central vasodilation.

This is the principle of the method which we have employed. While the principle is universally applicable, it has some technical limitations; but under proper conditions it has yielded very satisfactory results. So far we have confined ourselves mainly to the splanchnic circulation, as illustrated by the spleen and kidney. Theoretical objections may be urged against the choice of each of these organs. In the spleen, the trabecular muscles constitute a possible complicating factor; while the vascular control of the kidney is usually supposed to be in some respects *sui generis*. When, however, the results in the two organs coincide, they may fairly be considered as typical of the splanchnic vasomotor reactions; and this uniformity has been the rule in our work.

Vasomotor Reflexes. The vasomotor centre is easily influenced through the stimulation of afferent nerves. These reflexes are best investigated on curarized animals. During the rise of pressure which is produced by stimulation of the central end of the divided sciatic nerve, the flow of the perfusion fluid is practically always slowed (in the spleen, kidney, and opposite leg), showing the central vasoconstrictor stimulation. This slowing averaged 20 per cent.; and is about a third of that which may be produced by asphyxia; (incidentally, it may be remarked that the rise of blood pressure on sciatic stimulation is only about a fourth of that which may be produced by clamping the thoracic aorta).

The influence of the existing state of blood pressure on the vasomotor response is a rather interesting problem. Has the blood pressure any influence on the vasomotor centre? We have fully confirmed the observation of Porter and his pupils, that sciatic stimulation produces the same rise of pressure (averaging 30 mm. in our experiments) whether the pressure before stimulation was 160 or 100 or 60 mm. (below this level the response is impaired). In other words, sciatic stimulation produces the same absolute rise from all physiological levels. Accordingly, the "percentile" rise is the greater the lower the level of the blood pressure. A rise

of 30 mm. would amount to an increase of 50 per cent. if it occurred from the level of 60 mm.; but to only 25 per cent., if it occurred from the level of 120 mm. In other words, if the "percentile" change is the correct criterion, then the excitability of the vasomotor centre varies inversely to the blood pressure. If the "absolute" change is taken as the criterion, then the response of the centre is not affected by the level of the blood pressure (provided that this does not approach the "shock" level). Which, then, is the correct criterion? Our method permits us to give a direct answer to this question—the response is *not* affected by the level of the blood pressure, and the "absolute" change is therefore the correct criterion. This conclusion appears to us to be in consonance with the mechanical considerations.

We would emphasize, however, that our statement of the independence of the vasomotor centre from the blood pressure refers only to its response to stimulation, and not to the automatic tone of the centre. These two functions must not be confused. Indeed, we shall show that an acute fall of pressure, as produced by hemorrhage, may increase the automatic tone. An increased automatic tone would, of course, be vastly more efficient as a protective mechanism against low blood pressure than would increased excitability to unusual reflex stimulation.

The Vagus Reactions of the Vasomotor Centre. These can be studied to best advantage in dogs, since in these the vagus does not usually carry depressor fibers. *Stimulation of the central stump* (with both vagi divided) in curarized dogs gave results entirely analogous to those of sciatic stimulation. In no case was there any dilator effect in dogs (whereas dilation is almost constant in cats).

Sections of both vagi, in non-curarized dogs, causes a slight vasocontriction. This might conceivably be due to the rise of blood-pressure (which averaged 25 mm.). Atropinized cats, however, in which the rise of pressure is insignificant (averaging 14 mm.) gave the same results. The constriction is, therefore, presumably due to a slight asphyxial stimulation from the slowed respiration which follows vagotomy.

Stimulation of the Peripheral Stump of the Vagus (in the neck). The cardiac inhibition would lead one to expect the usual result

of cerebral anemia, namely, stimulation. Evidences of this were obtained, even when the inhibition was quite incomplete. The rapid escape of the heart from the stimulation, however, renders the demonstration somewhat unsatisfactory.

Stimulation of the Vagus Depressor in the Cat. While the depressor can be isolated to best advantage in the rabbit, the technical difficulties of perfusing the small organs of this animal have deterred us from its use. Our experiments on the depressor have, therefore, been done on the cat. The union of the depressor and vagal fibers in this animal might be thought to render it less favorable; in reality, however, it renders the occurrence of depressor reactions even more striking, for these must overcome the pressor reactions which tend to follow vagus stimulation, at least in the dog. In our experiments the fall of pressure on stimulation averaged 60 mm. The spleen and kidney both showed dilatation, *i. e.*, the typical effect.

Compression of the Thoracic Aorta and Injection of Suprarenal. It is universally assumed that the physiological stimulus of the depressor nerve is furnished by excessive blood pressure in the aortic arch. It may be a matter of surprise that the evidence for this widespread assumption is very slender and unsatisfactory; but such is the fact. If this is, indeed, the function of the depressor nerve, then the artificial raising of the blood pressure, either by aortic compression or by suprarenal injection, must quicken the perfusion flow.

Our experiments, however, show that the results are just the opposite. The typical effect of both these measures consists in moderate central vasocontriction. This not only in the dog, in which the depressor mechanism is, perhaps, relatively inactive; but also in the cat, in which depressor stimulation, were it present, could be easily demonstrated by our method.

If we are correct in our conclusion that the depressor nerve is *not* normally stimulated by high blood pressure, what then is its function? We have no answer ready to this question. G. N. Stewart has made the interesting suggestion to us that the depressor nerve might control the caliber of the systemic vessels chiefly in the interest of the *lesser* circulation. In view of the imperfect direct vasomotor control of the pulmonary vessels, this would be an ad-

vantageous arrangement for protecting the right heart and lungs against excessive pressure.

We should add, however, that prolonged or repeated aortic compression causes some injury to the centre, so that its response to subsequent stimulation is not as strong; and that as an after-effect of suprarenal injection, there may be some central vasodilatation as the pressure is falling toward normal.

As to the mechanism by which high blood pressure stimulates the vasomotor centre, we are very much in the dark. It may be simply through increased intracranial pressure. The constriction is probably not sufficiently powerful to have much functional significance.

Asphyxia. Partial and complete asphyxiation was produced by various methods, with identical results, namely, prompt and very powerful constriction. Even relatively slight asphyxia, such as is secured by breathing through a long tube, produces sufficient vasomotor stimulation to influence the outflow. With complete asphyxia, especially if it occurs suddenly and the centre is at all active, the constriction is vastly more powerful than we have been able to secure by any other means. Since this occurs as readily in curarized animals, the constriction cannot be attributed to convulsions.

The constriction outlasts death—or rather cardiac arrest—for a minute or so. Sometimes, indeed, it may not set in until the heart has stopped, and usually it becomes more pronounced during the fall of pressure which terminates the asphyxia. This is a very striking example of the failure of the systemic blood pressure to picture the state of the vasomotor centre.

If the asphyxia is removed, as by the timely administration of oxygen, the vasoconstriction also passes off; or if it is allowed to proceed to death, the centre becomes paralyzed in a short time, usually within two minutes, and the outflow is thus quickened.

Cardiac Arrest. Sudden cessation of the heart beat, secured by overdoses of strophanthus or by other means, produces the same extreme constriction as sudden asphyxia, the mechanism in the two cases being doubtless identical.

Cerebral anemia by occlusion of both carotid arteries also causes constriction—not very pronounced, but generally about as much as would correspond to the rise of the blood pressure. We have already discussed the results of cerebral anemia by cardiac arrest or by slowing the heart through vagus stimulation.

Hemorrhage. The effects of hemorrhage vary with its severity, and into this enters the condition of the animal as well as the absolute loss of blood, the vasomotor centre being successively stimulated, depressed, and paralyzed. In progressive bleeding the typical reactions of the vasomotor centre proceed in about this order:

Slight hemorrhage causes constriction, which becomes more and more pronounced, to a certain limit. The maximum constriction is observed when the loss of blood reaches, on the average, one-third of the total blood content, or 25 c.c. per kg., or when the blood pressure has fallen to about 95 mm. When the hemorrhage exceeds this degree, the constriction is replaced by progressive dilatation. When half the blood (37.5 c.c. per kg.) has been lost, on the average, or when the pressure has fallen to 30 mm., the dilatation has reached its extreme limit, *i. e.,* the paralysis of the vasomotor centre is complete.

If the blood is reinjected before this point is reached, the centre will recover its tone and the blood pressure will return to normal. If, on the other hand, the hemorrhage is prolonged beyond the point of maximal dilatation—in other words, until the centre is completely paralyzed—then the reinjection of the blood does not restore the tone of the centre. This means that the paralysis is irrecoverable, at least within a few hours. In this condition the re-injection of even a part of the lost blood may raise the pressure to about 60 mm.; but it cannot be brought above this level, no matter how much fluid is injected. Evidently the heart, in the absence of all central vasomotor tone, can only maintain the pressure at the level of about 60 mm. Nevertheless, an animal may live at least several hours with its vasomotor centre paralyzed in this manner.

It is worthy of remark that the vasoconstriction in hemorrhage is at no time anywhere near as great as that produced by cardiac stoppage. While cardiac arrest slows the flow by 75 per cent. or

more, the slowing in hemorrhages amounts to but 33 per cent., even in fatal cases. This is attributable to the slower course of the anemia, which allows the centre time to become injured before the stimulation becomes maximal. This fact, that injury of the vasomotor centre goes hand in hand with its stimulation, may have considerable practical significance.

Infusions of Normal Saline Solution. It is well known that the rise of pressure on saline infusion is usually only of moderate height and brief duration. This points to vasodilatation, which is confirmed by the increased volume of organs. This vasodilatation, however, need not be of central origin—it might be peripheral or purely mechanical, or possibly largely cardiac. As a matter of fact, our experiments show that intravenous saline infusions of 1 to 90 c.c. per kg. tend to stimulate the vasomotor centre, at least for the spleen. Central dilatation is altogether exceptional; it occurred but once in six experiments. More often there is no central effect.

There is almost complete parallelism between the response of the centre and of the blood pressure. Whenever the saline injection causes a somewhat lasting rise of pressure, there is central vasoconstriction. If the rise is not sustained, or if the pressure falls, the vasomotor centre also shows no response. The stimulation of this centre, therefore, has an important bearing on the therapeutic efficiency of such infusions.

The injection of saline solution into bled animals also causes constriction.

Our experience with overtransfusion of blood is still too limited to justify conclusions.

The Effects of Drugs. It may be permissible to refer to the results which we have obtained with drugs. We do not purpose to enter into this matter in detail, in the present paper, but will only mention the direction of their central action, without trying to distinguish whether the effects are direct or indirect:

Considerable constriction.	*Moderate constriction.*	*Practically negative.*
Strychnine (small doses).	Nitrites.	Pituitary.
Caffeine.	Curare.	Berberin.
Nicotine.	Suprarenal.	Hydrastinine.
Cyanide.	Hydrastis.	Atropine.
Aconite (toxic doses).	Hydrastine.	Aronite (small doses).
	Veratrum.	
	Cavadin.	

Dilatation.	*Variable.*
Chloroform.	Ergot
Strychnine (toxic doses).	

Conclusions. 1. A method is described for eliminating the complicating factors in the study of the vasomotor centre.

2. The most powerful stimulus to the centre is its asphyxia or anemia. Fairly powerful constriction is produced by stimulation of sensory nerves; by raising the blood pressure; by moderate hemorrhage; by saline infusion; by a considerable number of drugs, acting either directly or indirectly.

3. The centre is easily injured by asphyxia, anemia, and hemorrhage, and if the condition is severe even for a few minutes, the injury is permanent.

4. Direct depression of the centre is caused by chloroform, by toxic doses of the strychnine, and by stimulation of the depressor nerve. This nerve does not seem to be stimulated by high blood pressure.

5. It is interesting and worthy of remark that primary constrictor reactions are vastly more numerous than primary dilator reactions, but that many forms of primary constriction pass into secondary depression through injury of the centre.

BRONCHIAL ASTHMA AS A PHENOMENON OF ANAPHYLAXIS.

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It is now generally accepted that bronchial or idiopathic asthma is due primarily to a stenosis of the bronchioli. It is not necessary to dwell here on the particulars of this disease. For the purpose of this paper, however, the following facts may be mentioned. Asthmatic attacks occur only in individuals who are especially subject to it, that is in *asthmatics.* Furthermore, onset and disappearance of the attacks bear the character of capriciousness; also heredity seems to be an influential element in some instances. Finally, there is practically no pathological anatomy in this disease. On the basis of these facts, bronchial asthma is considered as a functional disease, which, according to the prevailing view, means a *neurosis,* hence also the term nervous asthma. From the symptomatology we shall mention here only the following points. By percussion it can be established that during an attack of asthma the lungs are overdistended. The auscultation reveals that there is a considerable *decrease* of the respiratory exchange of air despite the greatly *increased* efforts of the respiratory muscles.

There are two theories regarding the nature of the nervous origin of the bronchostenosis in asthma. One theory assumes that the stenosis is due to a vasomotor disturbance which brings about a swelling of the mucous membranes or of the submucous tissues of the bronchioli, causing thereby a narrowing of their lumen. The other theory assumes that the stenosis is due to a tonic contraction of the muscle fibers surrounding the finest bronchial tubes. At present the latter theory is accepted by most of the clinical writers,

especially since it was established by the careful physiological investigations of Einthoven[1] and of Brodie and Dixon,[2] that by stimulation of the peripheral end of the pneumogastric nerves a stenosis of the bronchi takes place which is due exclusively to a contraction of the muscle fibers, and not to the production of circulatory changes of any kind. According to this theory an attack is brought on by a stimulation of the bronchoconstrictor nerve fibers which run in the pneumogastric nerves. It is assumed that the stimulation takes places in some obscure way, mostly in the medulla oblongata; in some cases, however, it may be brought about by reflex way from some peripheral organ. At any rate, asthma, according to this view, is a nervous affection and has its origin in the central nervous system.

It is my intention to attempt to interpret the asthmatic paroxysm as a phenomenon of anaphylaxis, assuming at the same time that the process is a peripheral one. This attempt is based upon some very interesting facts recently discovered by Drs. Auer and Lewis[3] in the Department of Physiology and Pharmacology at the Rockefeller Institute. In order to understand clearly the points I wish to bring forward, permit me to make a few elementary remarks on the subject of anaphylaxis or hypersusceptibility.

Anaphylaxis is in an essential point the reverse of immunity. You all know what immunity means. Every physician is familiar with the fact that a patient who recovers from an infectious disease, typhoid, for instance, is less susceptible to a second infection from the same disease. The same applies to the effects of toxins. The experimental work of the last two decades brought ample evidence that the injections into an animal of non-fatal doses of toxins, for instance, the toxins of diphtheria or tetanus, make this animal more resistant—it immunizes it—against this very toxin. In other words, the passing through a definite infection or intoxication is the means of a decrease of the susceptibility of that animal to the specific infection or intoxication. There were, however, scattered facts which indicated that also the reverse of immunization may occur; that is, that instead of a decrease of susceptibility, an increase may

[1] Pflüger's Archiv, 1892, li, 367.
[2] Jour. of Physiol., 1903, xxix, 97.
[3] Jour. of Exper. Med., 1910, xii, 151; see also Jour. Amer. Med. Assoc., 1909, liii, 458.

occur. For instance, the passing through an attack of erysipelas seems to prepare the individual for recurrent attacks of this disease. The same is perhaps true also of pneumonia. In the extensive work on the immunization against toxins, several investigators recorded observations to the effect that an immunization led up to a hypersusceptibility.[1] However, about five years ago striking experiments became known which all at once raised this issue to a problem of considerable importance. Our president told us that the present annual meeting is the twenty-fifth of our Society, and pointed with pride to the good work which the members have contributed to medical science. Permit me, therefore, the historical remark that the striking and fundamental facts upon which the very interesting chapter of anaphylaxis rests were first observed and developed by members of our Association. In the course of his studies of the effects of diphtheria toxin and antitoxin upon guinea-pigs, Theobald Smith observed (1903) that by repeated injections of toxins these animals, instead of becoming immunized, sometimes manifested rather a definite increase of their susceptibility to the poisonous effects of the diphtheria toxin. These observations Dr. Smith communicated orally to Paul Ehrlich during his sojourn in this country. On his return to his Institute in Germany, Ehrlich caused one of his pupils, Otto, to investigate systematically this observation, who, in publishing his results, designated the fact of the hypersusceptibility as Theobald Smith's Phenomenon. Simultaneously, and independently of any other observers, the striking phenomenon was observed and extensively investigated by Dr. Rosenau in conjunction with Anderson.[2]

The fundamental experiment which brings out this phenomenon in a striking manner is as follows: A guinea-pig receives a subcutaneous or intraperitoneal injection, let us say, of a small dose of horse serum. The injection produces apparently no effect; the

[1] We may mention here: Behring (1893), Richet (1902), Arthus (1903), Wolf (Eisner) (1904), Pirquet and Schick (1905).

[2] The publications of Otto, as well as those of Rosenau and Anderson, appeared in 1906, and I am at present unable to state whether and which one of the publications was slightly ahead of the other. But I can bear witness to the complete independence of the observations of Rosenau and Anderson, because, in December, 1905, Dr. Rosenau was kind enough to communicate to me their remarkable experience, and we discussed the possible meaning of the phenomenon.

animal remains perfectly normal. When, however, a few weeks later, a second injection of horse serum is given to this animal, let us say 1 c.c. of the serum, and given intravenously, the animal dies within a few minutes in a striking manner. This is an absolutely reliable experiment which never fails. Now, you observe that the result as described here was accomplished not with a bacterial secretion, a diphtheria or tetanus toxin, or an endotoxin of any other bacteria, but simply with normal horse serum which seems to be innocuous in its first injection. In fact, this hypersusceptibility can be produced with such harmless proteins as egg albumin, milk, or some vegetable protein—edestin, for instance.[1] A striking feature of this phenomenon is that it is strictly specific; if the first injection was made with horse serum, the phenomenon will occur only when horse serum is used in the second injection, or if edestin was used in the first injection, only a second injection of edestin is capable of producing the fatal phenomenon. Let me now say a word about the origin of the term anaphylaxis. It was created by Richet some eight years ago. In studying the effects of a poison which he isolated from *actinia* he distinguished two opposite actions, one which produces prophylaxis (immunity) and another which produces anaphylaxis (hypersusceptibility). The term anaphylaxis found general acceptance.

Now, let us remember first of all that for the production of anaphylaxis two stages, two separate processes, are necessary. The first part consists simply in an injection into the animal body of some foreign proteid. It produces practically no visible effect, but it sensitizes the organism; we call it, therefore, the *sensitizing* injection. It need not be an intravenous injection; an incorporation of the proteid in any other manner will have the same effect. The quantity of the proteid is also of no special importance; a very minute dose of the proteid sensitizes an animal. The second part consists, as stated before, in a repeated injection of the same proteid; this is the *toxic* injection. The effect of this injection is, indeed, most striking, especially when it is given intravenously. The quantity is also of some importance; the larger the dose is, the more prompt is the

[1] First successfully employed by P. A. Lewis.

effect. The second injection should not be given too soon after the sensitizing injection; the interval between the two injections should be at least twelve or fourteen days.

The sensitizing effect may be transmitted from the mother to the offspring, which, however, may gradually dwindle away. The acquired sensitization leaves a long-lasting impression; even after years a second injection is capable of producing a definite toxic effect. The effect, however, is not always fatal and as striking as described above. When the second dose is not sufficiently large, or when administered in a less effective manner, the guinea-pigs may recover from the "anaphylactic shock" (as the violent attack is often designated) or the attack may set in with less violence.

We now come to a discussion of the point which interests us here mostly, namely, the character of the attack. From the start, all observers agreed that the death of a guinea-pig in an anaphylactic attack is due to respiratory failure. The attack consists in exaggerated respiratory efforts and manifestations of profound dyspnea. Most of the writers assumed that the cause of this fatal respiratory disorder is located within the central nervous system, some insisting upon especially that the respiratory centre in the medulla oblongata is the affected focus. Gay and Southard,[1] who have done meritorious work on the problem of anaphylaxis, are emphatic in their claim that the fatal respiratory phenomenon is due to a hyperstimulation of the respiratory centre. Although Gay and Southard noticed that the lungs of guinea-pigs dying in anaphylactic shock are "emphysematous," they considered this condition as being only a secondary effect of the violent inspiratory contractions of the diaphragm, the primary cause of the attack being, as stated before, the overstimulation of the respiratory centre.

The recent investigations of Auer and Lewis, however, have, in my opinion, definitely established the true cause of the anaphylactic shock in guinea-pigs. In the first place, they have established that the lungs which became greatly distended with the onset of the attack remain in a distended state even after their complete removal from the thoracic cavity after the death of the animal; in fact, the

[1] Jour. of Med. Research, 1908, xix, 22.

lungs do not collapse even when cut into pieces. An anatomical study of the lungs demonstrated that the distention is due neither to emphysema nor to pulmonary edema. Furthermore, the typical condition of the lungs remained the same even if the second, toxic injection of the serum was administered while the animal was under the influence of curare (and the life kept up by artificial respiration); that shows that the distended state of the lungs cannot be simply a secondary effect of the violent contractions of the diaphragm. The real character of the dyspnea was revealed by the fact that during the anaphylactic attack the lungs could not be further inflated by artificial respiration; that is, air could not pass through the bronchi into the alveoli while the respiratory efforts produced at the same time a strong negative pressure in the pleural cavities. Finally, Auer and Lewis have established that the anaphylactic attack takes place in animals with destroyed central nervous system exactly in the same way as in normal animals, which proves that the process is of peripheral origin. In other words, Auer and Lewis have definitely proved that the cause of the acute anaphylactic death of guinea-pigs is a stenosis of the bronchi due to a peripheral process. This process consists, Auer and Lewis believe, in a constriction of the bronchi, due to a tonic contraction of their muscle fibers. It is sure that these contractions are not brought about by central impulses. Whether these contractions are brought about by a stimulation of the muscle fibers themselves or of the nerve endings, this question Auer and Lewis did not decide for the present. They have discovered the important fact that in many cases *the anaphylactic attack can be prevented by a previous injection of atropine.* This fact would indicate, according to the accepted view, that the nerve endings are responsible for the attack. On the other hand, Auer[1] recently found that the attack would set in even in such animals in which the vagus nerves were cut a long time before the second injection. The nerve endings, therefore, must have been degenerated previous to the anaphylactic attack. We may add here that the important results of Auer and Lewis were already confirmed by Anderson and Schultz[2] and by Biedl and Kraus.[3]

[1] Proc. of the Soc. of Biol. and Med., 1910, vii, No. 4.
[2] Proc. of the Soc, for Exper. Biol. and Med., 1910, vii, 32.
[3] Wien. klin. Woch., 1910, xxiii, 385.

The following facts, observed by Auer and Lewis, are of special interest to us here. In an anaphylactic attack the bronchi are constricted; no air can pass into the alveoli, nor can it escape from it; and the lungs are greatly distended and cannot collapse. It was shown that the constriction of the bronchi is of a peripheral and not a central origin. Now, exactly similar symptoms we meet with in so-called nervous asthma. During the attack the bronchi are constricted; air passes through them only with great difficulty. Is asthma a nervous process and of central origin, as is generally assumed, or is it an anaphylactic phenomenon and essentially of peripheral origin? That is, may we not assume that *asthmatics are individuals who are sensitized to a definite proteid substance and the asthmatic attack takes place when the same proteid substance invades the body in the same manner?* For one form of asthma, this has been established experimentally, and that is, for the hay fever asthma. As it is now well known, hay fever is due to the toxalbumins of pollen of some plants. When such a toxin is injected subcutaneously into a normal individual, it causes no effect whatsoever. If, however, a minute quantity of it is injected into an individual who is subject to hay fever, in a short time all the symptoms of hay fever appear, and among them a definite attack of asthma. This can only mean *hay fever subjects are sensitized to a specific proteid of the pollen of a definite plant, and that whenever the same proteid invades these individuals in some way or other the result is an anaphylactic attack, which among others manifests itself in the form of asthma.* May we not explain all other forms of asthma in the same manner? According to this view, to repeat again, an asthmatic is an individual who is sensitized to a definite substance, and an asthmatic attack sets in every time when this substance manages in some way to enter into the circulation of that individual. We must bear in mind that even in the crude manner of our experiments a very minute quantity of the specific proteid is sufficient for the sensitization as well as for the intoxication. In the actual processes which take place in nature the effective doses may be infinitely small, and it may well be possible that the minute quantities contained in the emanation from horses, cats, or guinea-pigs are sufficient to act as a toxic dose and call forth the non-fatal stenosis of the bronchi evidently present

in a human asthmatic attack. Perhaps certain digestion products of the proteins become now and then absorbed into the circulation from the alimentary canal in some cases in an abnormal stage. Such an absorption may have little or no influence upon normal individuals, but will call forth an anaphylactic attack, that is, an attack of asthma, in an individual sensitized just to this protein product. We need not attempt to work out the details of our theory. Our knowledge of the anaphylactic process is yet too young and too scanty for such an undertaking; any application in detail will surely have to be rearranged. But with our theory in mind, a future study of cases of asthma might bring to light definite causal relations, just as it happened in the studies of hay fever. For the present, the following parallel facts may be recalled to mind. The sensitization to anaphylaxis may be hereditary or acquired; so is the disposition to asthma either hereditary or acquired. Anaphylaxis is specific; animals sensitized to a definite proteid can be intoxicated only by that proteid. The same seems to be true also for asthma. This is certainly true for the hay fever asthma. Individuals who suffer from hay fever in the spring due to the grass pollen are not subject to the autumnal attacks which are caused by the *ragweed* pollen. But the specificity seems to hold good also for other cases of asthma. For instance, individuals who get attacks of asthma in the presence of cats do not get it by the emanations from horses or from guinea-pigs. A most interesting and valuable point is the fact that atropine, which relieves asthma, relieves, as was discovered by Auer and Lewis, also the anaphylactic attack. On the basis of the identification of the two phenomena, there is an encouraging outlook for therapeutics of anaphylaxis as well as that of asthma. But I shall not indulge in a further discussion of the details of our subject.

Summary.—It is generally agreed that the so-called nervous asthma is due to a stenosis of the bronchioli. It was discovered that the so-called anaphylactic shock is due also to a stenosis of the fine bronchi. The theory is here offered that asthma is an anaphylactic phenomenon; that is, that asthmatics are individuals who are "sensitized" to a specific substance and the attack of asthma sets in whenever they are "intoxicated" by that substance.

It was proved that the anaphylactic attack is of peripheral and

not of central origin. It is therefore suggested that also the so-called nervous asthma is due to a peripheral and not a central cause; in other words, "nervous" asthma is not a neurosis.

On account of the capriciousness of the onset and course of asthmatic attacks, as well as on account of the absence of pathological anatomical changes in this affection, asthma was considered a functional disease, and hence a neurosis. From our point of view asthma is still a functional disease, but not a neurosis. We have, therefore, a significant instance in which a functional disease need not be of nervous origin.

ON THE COMMONER TYPES OF FUNCTIONAL CARDIAC MURMURS.

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The question as to the significance of cardiac murmurs is often one of the gravest which is brought before the physician—and the surgeon. Examiners for insurance companies, medical boards of the army and navy, school physicians, surgeons on the eve of an operation, meet daily with individuals in whom there are detected cardiac murmurs of varying character unassociated with evidences of functional disturbance. And if, in the course of the examination, the patient gain knowledge that he has a cardiac murmur, the question as to its nature and significance is often referred to one or more colleagues of the original examiner. The experienced clinician, meeting with many such cases, learns soon to pass almost unconsciously over the commoner and more obviously unimportant of these murmurs, making, perhaps, no comment on them even in his private records—and is genuinely surprised to find that his younger and less experienced colleague is unfamiliar with that which to him is too obvious to mention. He forgets that it is only long clinical experience that brings confidence in such matters, and that under the imperfect methods of clinical instruction which have prevailed in the past, and, unfortunately, still prevail to a considerable extent in America today, a large proportion of physicians enter their profession with a very limited practical experience.

Upon the subject of "functional," "accidental," "anæmic," or "hæmic" murmurs, as they may chance to be called, there is a large literature rich in observation, but especially rich in hypothesis. In many of the studies the hypothetical considerations have overshadowed the clinical description.

It cannot be denied that there are many cases in which the significance of a murmur can be determined only by time and observation. That, however, which seems to us to have been hardly enough emphasized is that there are certain clinical pictures of functional cardiac murmurs which are really rather easily recognizable. To consider some of these commoner pictures is the main object of the present communication.

What is the significance of a cardiac murmur in general? By what mechanism are cardiac murmurs produced? Rather broad questions, one may say, and yet the questions may, for the most part, be answered in a relatively simple manner. The overwhelming majority of cardiac murmurs are probably the result of fluid veins arising beyond a point of constriction, or just beyond a more or less fixed point, through which the blood passes into a vessel of considerably larger size, or capable of greater distention. At such points it is obvious from the simplest physical consideration that murmurs should arise the more readily, the more rapid the current, and the less viscous the fluid; and, moreover, that they should be transmitted in the course of the current.

Nothing is simpler than the illustration of these points to a class by means of rubber tubes attached to a water tap. The character of the murmurs which arise with stenoses or insufficiencies of the four cardiac orifices are familiar enough to all, and the explanation of their manner of origin and conduction is simple enough. The manner of origin and the conduction of all the ordinary cardiac murmurs, with the exception of stenoses of the auriculo-ventricular orifices, may be illustrated remarkably well in the living dog's heart tube, and few demonstrations are more illuminating than the production of an artificial mitral insufficiency, where one may hear, on auscultation, a soft systolic murmur at the apex of the left ventricle, while in the left auricle, immediately beyond the valves, there is a marked thrill and a murmur of the very highest degree of intensity.

If it be easy to see why, in disease, murmurs arise, it is difficult, indeed impossible, to explain why, at certain points in the heart, murmurs *are not always present* in the normal individual. That, under ordinary circumstances, no murmur should be produced by the entrance of blood from auricle to ventricle, is perhaps not re-

markable when one reflects upon the large size of the orifice—so large, after all, that auricle and ventricle represent in diastole practically one cavity—and the relatively low pressure under which the blood passes from auricle to ventricle. But when one considers the normal emptying of the ventricle, the structure of the aortic and pulmonic rings, and that of the vessel beyond, the wonder is not that systolic murmurs at pulmonic and aortic orifices often occur, but, as has been well said before, I think by Dr. Broadbent, that they are not always present. A ventricle contracting with considerable force, throwing a large quantity of blood through the fibrous ring at the root of the aorta or pulmonary artery, a ring which is practically indistensible, into a vessel beyond capable of great dilatation—here we have elements which one might well fancy should produce always a relative stenosis sufficient to result in fluid veins beyond the point of relative constriction, *i. e.*, the normal ring. That with a dilatable aorta, an unusually large quantity of blood thrown out of the ventricle with greater force through a normal ring may produce murmurs, and loud murmurs, is clearly shown in aortic insufficiency, especially in young individuals. How often, in such cases, a mistaken diagnosis of aneurysm is made is familiar to all clinicians. But, as we all know, there is a variety of conditions in which, without disease of the valves or muscle of the heart, murmurs are audible. Certain of these functional murmurs are so constant in their character as to be immediately recognizable. There are, it seems to me, at least three such clinical pictures.

1. The basic, commonly called "pulmonary" systolic murmurs.

These murmurs, which are usually rather soft in character, and generally associated with an element of the first sound, are best audible in the third left interspace, but are often heard with less intensity all over the heart. If heard at the apex, they are usually limited to the recumbent position, disappearing when the patient stands up, while even at the base they are of considerably less intensity and may disappear in the erect posture. As pointed out by Janeway,[1] these murmurs are greatly intensified, often becoming loud and rough on forced expiration. On inspiration, however, they become

[1] Trans. Assoc. Amer. Phys., 1896, xxi, 61.

feebler, and when the breath is held after a deep, full inspiration, the murmur usually vanishes. Such murmurs, absent at all other times, may be brought out in a considerable number of individuals by forced expiration. They are common in young people, and are, as a rule, unassociated with any other form of cardio-vascular abnormality. This phenomenon forms a fairly definite clinical picture, and may be recognized readily.

2. Systolic murmurs limited to or heard with greatest intensity at the apex, but audible only in the recumbent posture.

Murmurs such as these are very common in healthy young men and women. They are commoner, perhaps, in nervous or thin, emotional people, but are often found in robust youths and girls. The murmurs may be very slight and feeble, or they may be fairly loud; they do not replace the first sound which in itself, is distinct, sometimes well defined, sometimes prolonged. The murmur may be transmitted for some little distance into the axilla, and is commonly accentuated on the left lateral posture; indeed, it is not infrequently heard only in this posture. On standing up, or sitting, the murmur entirely disappears. There is no further evidence of cardio-vascular defect. Such murmurs may be heard all over the cardiac area—sometimes they are loudest in the pulmonary area. In the erect posture, however, they clear up at the apex, leaving only the pulmonary systolic which, as has been said, disappears on inspiration.

3. Cardio-respiratory murmurs.

As is well known, there has been much discussion as to the frequency of murmurs arising in the respiratory tract, but dependent upon cardiac action, and suggesting, on cursory examination, a true endocardial sound.

Potain[1] sought to explain all non-organic heart murmurs by the cardio-pulmonary hypothesis.

To the careful observer the existence of cardio-pulmonary murmurs can hardly be a question of doubt. They form, however, a definite class and are usually easily recognizable. They are commonly systolic in time, but rather late, occurring an instant after a

[1] Clinique médicale de la Charité, 8°, Paris, 1894, Masson.

clear-cut first sound. They are often short and of a character different, on analysis, from that of the ordinary soft intracardiac murmurs. The important point is that they are limited to one phase of the respiration, disappearing, as a rule, when the breath is held. The commonest form is that which is heard with the several beats occurring during inspiration. In these cases careful attention reveals clearly that the murmur is simply an intensification of the respiratory murmur, and sharply limited to the period of ventricular systole. These murmurs are often more intense on effort with rapid, forceful, cardiac action, and on deep breathing.

What is of special importance is the fact that *they are often heard with great intensity in the back.*

Cardio-respiratory murmurs are by no means limited to inspiration. They may occur at other phases of the respiration as well, and sometimes may be noticeable when the breath is held. In many instances, no matter at what phase of the respiration it may be present, a cardio-respiratory murmur may be recognized by a distinct difference between its timbre and that of the usual endocardial murmur—its superficial, short, rustling character, and especially its lack of direct association with one of the cardiac sounds, which it *accompanies rather than modifies.* This may be appreciated by making a young individual take vigorous exercise and listening when his heart is beating rapidly and forcibly and the respiration is accelerated. Here, a short post-systolic whiff is not uncommonly heard, usually during the middle of inspiration—a sound which, on careful study, is obviously of pulmonary origin. Familiarity with the commoner post-systolic cardio-respiratory murmurs may not infrequently bring comfort and assurance to the examiner who meets with similar sounds at other phases of the respiration.

One fact which again should especially be emphasized is that cardio-respiratory murmurs are not infrequently audible in the back, and may here give rise to serious misapprehension by the unskilled observer.

Now, in addition to these three more definite types, there are observed in healthy individuals many cardiac murmurs which experience and time may and do justify the clinician in regarding on the first or on later examinations as of functional character. The

judgment as to the significance of many of these sounds must be formed in the individual case. Such decisions are often of the most delicate and important duties which fall to the physician.

In a general way, murmurs which are limited to a single phase of the respiration may be regarded as of no pathological significance. Soft systolic murmurs which occur at the apex as a slight whiff, after a first sound which seems clean-cut and of a normal character, in hearts which are of a normal size and without undue accentuation of the pulmonic second sound, may, as a rule, be regarded as functional, even if they do persist in the erect posture and on full inspiration. These cases, however, do not form a definite recognizable clinical picture, as in the three groups above mentioned.

Again, there are instances in which systolic functional murmurs at the apex are present in the erect posture alone and absent in the recumbent posture. This condition, on which Potain insists, is, in the experience of the author, rare. In general, however, it may be said, with considerable assurance, that heart murmurs limited to a single phase of the respiration, or heard in one position of the body alone, are, in the great majority of cases, quite devoid of pathological significance.

There are, however, other murmurs unassociated with essential and incurable cardiac lesions, which are commonly considered in the same class as those already mentioned. This does not seem to the writer fitting. He prefers to consider them apart, as they are, after all, associated with definite, though perhaps not serious, disease. Among these are:

1. *Those murmurs associated with anæmias of all sorts.* These are, on the one hand, (*a*) soft systolic murmurs heard at the base, more commonly at the pulmonic than at the aortic orifice, but frequently at both. In these individuals the pulse is often large and soft, and the throbbing of the arteries is generally noticeable. (*b*) Systolic murmurs at the mitral and tricuspid orifices: These murmurs are also soft and blowing, sometimes, however, largely replacing the first sound. They are not infrequently transmitted to the axilla, or even to the back, and the second pulmonic may be somewhat accentuated, while commonly the heart is slightly large.

2. *Systolic apical murmurs occurring especially in the course of an acute infectious disease* (acute rheumatism, and typhoid fever

especially), where, however, there may be relatively little anæmia. In these patients the first sound is usually dulled and may be wholly replaced by the murmur. Here, again, there is generally a slight cardiac enlargement; the murmur may be transmitted to the axilla and the second pulmonic may be slightly accentuated. These two conditions have been considered in a separate class because, although there may be no valvular disease, yet the slight enlargement of the heart, the enfeeblement of the first sound, the accentuation of the second pulmonic, the behavior of the heart on exertion, justify one in assuming the existence of a true weakness of the heart muscle with dilatation of the orifices and secondary mitral, and perhaps tricuspid insufficiency. The general condition of cardiac weakness and secondary mitral and tricuspid insufficiency form a picture perfectly distinct from that presented by normal individuals with cardiac murmurs of the three first mentioned types with which we are concerned.

Systolic murmurs are not uncommon at the apex in exophthalmic goitre. But here, again, there is generally a distinct cardiac enlargement, and there is much evidence to lead one to believe that these murmurs are the result of true insufficiency of the mitral ring dependent upon dilatation.

Transient Aortic and Pulmonic Insufficiency. Before discussing the *raison d'être* of these various functional murmurs, it may be well to say a word as to the occurrence of murmurs indicating aortic and pulmonary insufficiency in the absence of disease of the valves. Aortic insufficiency of muscular origin is only to be recognized by prolonged observation of the case. The writer has, however, met with a number of cases sufficient to convince him of its actual occurrence.

In two instances after typhoid fever he has seen the development and disappearance, with complete convalescence, of a characteristic murmur of aortic insufficiency, associated with slight cardiac enlargement and a noticeably collapsing quality of the pulse.

He has also met with a similar condition in two cases of exophthalmic goitre. Both of these cases are sufficiently remarkable to deserve a brief note.

The first case was that of a trained nurse who, showing marked

symptoms of exophthalmic goitre, consulted me with regard to operation. As there was evidently double mitral valvular disease, together with an aortic insufficiency, operation was not advised. The wise patient, however, took matters in her own hands, and repaired to Dr. Olmsted, of Hamilton, who performed a thyroidectomy, which resulted in complete recovery. On examining the patient some six months later, I was surprised to find that all traces of aortic insufficiency had disappeared. This nurse has since then been doing active work for ten years. Last year I had the privilege of examining her again, and found evidence of old, double mitral disease in perfect compensation, but no signs of an aortic insufficiency.

The second case was that of Mrs. S., aged thirty-eight years, who first entered the hospital in March, 1901, with distinct symptoms of exophthalmic goitre. No cardiac abnormality was noted. She returned in June, 1905. At this time there was some irregularity of the heart and a slight systolic murmur all over the area. The cardiac apex impulse was 10 cm. from the median line. The urine showed a trace of albumin and a few hyaline and finely granular casts.

Two years later, in November, 1907, the patient was seen again. Dyspnœa and œdema of the feet had come on nearly a year before and had been gradually increasing. She was anæmic; the pulse was collapsing and rather irregular, about 100. The heart was large, the apex impulse 12 cm. from the median line. There was a systolic murmur heard all over the cardiac area, loudest at the base and transmitted upward into the carotids. A slight diastolic murmur was distinctly heard along the left sternal margin. The second pulmonic sound was accentuated.

The patient entered the hospital, where she remained for nearly three months. Rest was followed by but little improvement. The heart increased in size, the apex impulse being recorded as 145 cm. from the median line. The urine showed a trace of albumin and a few hyaline and granular casts.

In December and January a large part of the thyroid was removed in two operations. This was followed by some improvement, but the œdema never wholly disappeared. At the end of February she left for home, improved but in a condition far from satisfactory. At the time of departure the apex impulse was 145 cm. from the

midsternal line. The systolic murmur was still heard all over the area, but the diastolic murmur was no longer audible.

About nine months later the patient was again seen in Atlanta. She had improved in many ways, was able to walk about, and was free from œdema. The heart was somewhat irregular—about 100. There were no cardiac murmurs, but there was a slight proto-diastolic gallop at the apex. In October, 1909, a year later, she walked into my consulting room, apparently well. Her pulse was still a little rapid—about 100—and somewhat irregular. The apex was 2 or 3 cm. nearer the median line (11.5 to 12). There was a soft basic systolic murmur, barely audible, but no murmur at the apex and no trace of a diastolic murmur at the base or along the sternal border. The patient was seen again in June, 1910, after the reading of this paper; she remained in good condition.

A most interesting case of similar character, following tonsillitis and polyarthritis, came under the observation of the author last year. J. L., a colleague and friend, consulted him on September 3, 1909. He had been in bed for two weeks with polyarthritis following tonsillitis. He looked pale and worn out. The pulse was slightly abrupt, and the heart a little large. The apex impulse was in the fifth space, 9 cm. from the median line, and the dulness extended 4.2 cm. to the right. There was a slight diastolic murmur in the aortic area and along the left sternal border, although the second aortic sound was fairly sharp. A year before, the writer had examined the heart, finding no abnormalities. An endocarditis was feared. A month later, however, the heart was somewhat smaller. The pulse no longer collapsing, and the aortic murmur was wholly gone. Six months after this he was in good general condition. The apex was 8 cm. from the median line; a soft systolic murmur was heard all over the cardiac area in the recumbent position, disappearing at the apex in erect posture and at the base on deep inspiration. The diastolic murmur had remained absent.

The observations of Hugh Stewart (unpublished observations) have proved the importance of the part played by the ring of muscle below the aortic valves in the closure of the orifice. And just as Stewart has been able to produce an aortic insufficiency by mechanical injury to this ring of muscle without lesion of the valves, so, in

some cases, it is but natural that a weak and diseased heart muscle should result in aortic as well as mitral insufficiency.

Pulmonary insufficiency independent of valvular disease is also a condition commoner than has been generally recognized. It is met with, as Graham Steele has pointed out, in connection with cases of dilatation of the right ventricle usually following old mitral disease, and is associated with a soft diastolic murmur heard along the left sternal margin, in much the same area as that occupied by the murmur of aortic insufficiency; the murmur has also a similar character. One may suspect the nature of such a murmur by the absence of other signs of aortic disease (character of the pulse and of the second aortic sound at the base and in the carotids), the presence of marked dilatation of the right ventricle, and sometimes by the disappearance of the sound with improvement in the patient's condition. That such murmurs may be associated with dilatation of the pulmonic orifice in absence of aortic changes has been proved frequently by necropsy. Two cases of this character have already been demonstrated at our clinical and pathological conference during this term. It goes, however, without saying that these murmurs are indicative of pathological changes in the heart muscle—changes from which there may be improvement, and perhaps, indeed, actual recovery, as in some cases of exophthalmic goitre, or after acute infections. They do not, however, represent purely functional murmurs in normal individuals.

To return to the commoner forms of truly functional murmurs in normal individuals, viz.:

1. The basic "pulmonary" systolic murmurs.
2. The apical systolic murmurs disappearing in the erect posture.
3. The cardio-respiratory murmurs.

From careful observation we know that these murmurs have practically no pathological significance. Can we explain their appearance?

As to the first form—the *basic systolic murmurs* over the conus or pulmonary artery—there are various possibilities. As has been said, the structure of the pulmonary artery and orifice, as well as that of the aorta—a practically indistensible fibrous ring with a highly distensible vessel beyond—is such that it is remarkable that systolic murmurs are not always present.

McCallum and the writer[1] have observed that in dogs it is extremely easy to produce a systolic murmur just beyond the pulmonic ring, following hæmorrhage. Here the excursions of the pulmonary artery were generally very large; in other words, the vessel was relaxed or the volume of blood thrown into the vessel with each systole was large. This was also true in cases where, after hæmorrhage, salt solution had been infused. Under these circumstances also the ventricular action appeared to be rather abrupt. Now, in anæmia in general there is a rather low blood pressure. Furthermore, the changes in the blood itself might be expected to favor the appearance of murmurs (diminished specific gravity and viscosity). Especially important, however, are the observations of Plesch,[2] who has shown that in anæmia the rate of blood flow per minute is greatly increased; more than this, the volume of blood thrown into the vessels with each ventricular contraction is larger than under normal circumstances. The conditions, then, which are present in anæmia—increased quantity of blood thrown with each systole through the aortic and pulmonary rings, which, as has been said, are more or less indistensible, the changes in the blood itself, and the relaxed condition of the vessels—are exactly those which one might postulate for the production of basic systolic murmurs.

The explanation, then, of many systolic murmurs in aortic and pulmonic areas in anæmia is simple enough.

It is a question, however, whether any of these conditions play a part in the production of the basic murmurs so common in healthy young individuals. It is significant that these murmurs are heard best on the left side of the sternum, and in the third space, rather below the pulmonary orifice. It is also remarkable that they are increased or induced by expiration, and diminished or obliterated by inspiration. These facts suggest another explanation.

Now, McCallum and the writer observed that in dogs with an exposed heart it is extremely easy to produce a murmur by very

[1] Experimental Studies on Cardiac Murmurs, Amer. Jour. Med. Sci., Philadelphia and New York, 1907, cxxxiii, 249.

[2] Sauerstoffversorgung und Zirculation in ihren Kompensatorischen Wechselbeziehungen, Verhandl. d. XXVI Kong. f. inn. med., Wiesb., 1909, 299; also, Bestimmung des Herzschlagvolumens, Deutsche med. Wochenschrift, 1909, xxxv, 239.

slight pressure on the conus arteriosus with the bell of the stethoscope. Such pressure resulted in a thrill and murmur beyond this point. May it not be, then, that the pressure exerted by the chest wall against the pulsating conus arteriosus may often be sufficient to result in such a murmur? With inspiration the interposition of a cushion of air-containing lung equalizes the pressure, removes the cause, and the murmur ceases. With age and increased volume of the lungs the murmur is less frequent. This hypothesis, while unproved, has seemed to me that which is most applicable to the condition. Janeway,[1] in a discussion of our paper, calls attention to the frequency of expiratory systolic murmurs at the base, and suggests pressure as a cause.

The cause of the *cardio-respiratory, inspiratory systolic murmurs* is obvious enough. The reinforcement of the inspiratory murmur with each systole is due to the accentuation of inspiration during ventricular contractions, and the sound dependent on this ought to be more marked, the more forcible and abrupt the contraction and the larger the quantity of blood expelled. As has been said, exercise may and often does exaggerate this phenomenon.

As to the cause of the *systolic apical murmurs* heard in the recumbent and left lateral posture, the writer can only express an opinion in agreement with that of Henschen,[2] but unsupported by experimental evidence. He has always regarded these murmurs as indicative of a true mitral insufficiency because of the location in which they are heard, because of their occasional transmission outward, and because of the general similarity of the sound to that heard in true mitral insufficiency. Such a mitral insufficiency dependent on position alone, if it be a mitral insufficiency, is, however, a perfectly normal phenomenon.

Whatever the cause of these phenomena, it seems to him that these three forms of murmurs—(*a*) the basic systolic murmurs increased on expiration, (*b*) the apex systolic murmurs limited to the recumbent posture, (*c*) the cardio-respiratory, inspiratory systolic murmurs—form three clinical pictures which are fairly distinct and apparently of no pathological significance.

[1] Trans. Assoc. Amer. Phys., Philadelphia, 1906, xxi, 61

[2] Ueber systolische functionelle Herzgeräusche C. r. XVI Cong. int. de méd., Budapest, 1909, vi, Méd. interne, fasc. I, 221.

Frequency. How frequent are these murmurs in normal individuals? *Basic systolic murmurs* are, as is known, extremely common. It would be interesting to know how often it might be possible to produce these murmurs by forced expiration in a given number of individuals. The writer, however, has no figures to offer based on any large number of observations.

Cardio-respiratory Murmurs. Cardio-respiratory murmurs, of the kind of which we have spoken, are not rare, but by no means as frequent as the last mentioned class.

A point of particular interest and importance is the frequency with which *systolic apical murmurs* of undoubtedly functional character are audible in practically normal individuals.

Last year the writer had occasion to examine a large number of healthy young people in connection with studies of the third heart sound. In all these individuals special note was made as to the presence of systolic murmurs disappearing in the erect posture. Of 218 cases in the first four decades of life, 73, or about one-third, showed systolic murmurs at the apex in the recumbent posture, murmurs which disappeared in the erect attitude. As a rule, these murmurs were heard all over the cardiac area, but loudest at the base in the pulmonic area.

The following table illustrates their frequency by decades:

Table Showing the Frequency of Apical Systolic Murmurs in Healthy Individuals.

Decades	1	2	3	4
Cases	39[1]	98	55	26
Murmurs present	22	35	12	5

It will be seen that in the first decade 56 per cent. of these individuals showed systolic apical murmurs in the recumbent position; 35 per cent. in the second decade; 21 per cent. in the third; 19 per cent. in the fourth. These murmurs were, of course, usually associated with the common basic systolic murmur, of the presence of which no special note was made.

Especially interesting are the statistics of the examination of thirty robust boys who were studied at one of the best conducted of schools, situated in the country just outside of Baltimore. These

[1] No cases under three years of age were examined.

boys were all in the second decade and in apparently excellent physical condition. In none of them was there the slightest subjective or objective evidence of cardiac involvement.

Eighteen of these thirty boys, however, showed cardiac murmurs of one sort or another.

In thirteen a soft systolic murmur was heard all over the cardiac area when in the recumbent or left lateral posture.

Three showed basic systolic murmurs disappearing on full inspiration.

One showed a basic systolic murmur present in the recumbent posture alone.

One showed a basic systolic with no evident change on respiration. This, from its character and position, and from the absence of any other suggestion of cardiac involvement, was regarded as certainly functional.

To many, perhaps, these considerations may seem *altbekanntes*, and yet the number of men who are refused by insurance and mutual benefit organizations, whose career is cut short in army and navy because of a lack of appreciation by over-conscientious examiners, of just these points, is really large.

In one year the writer had had occasion to examine fourteen young men between the ages of eighteen and twenty-four, the condition of whose hearts had been questioned by the careful examiners of applicants for a certain well-conducted organization. In one of these subjects there were marked extra-systolic irregularities. One was a nervous young man with a rather rapid heart. All the others, twelve in number, showed various forms of the three types of functional murmurs of which we have spoken, without other serious evidence of cardiac defect.

Such experiences emphasize the fact that it is important to realize that cardiac murmurs are, in many instances, normal phenomena, that under some circumstances and conditions they are to be expected in normal individuals, and that certain of these truly functional murmurs are not difficult to recognize and to account for.

It is also important to distinguish these true functional murmurs from those other murmurs to which the same term is often applied,

murmurs which depend on valvular insufficiencies due to pathological weakness of the heart muscle.

Lastly, it is well to remember that it is only when murmurs occur in certain localities or in more or less definite relation to the heart sounds, or when they are associated with evident anatomical or functional derangement, that they are necessarily of pathological significance.

In conclusion, then, the writer would urge:

1. That a cardiac murmur is but one, and sometimes an unimportant one, of the links in the chain of evidence leading to the recognition of disease of the heart.

2. That certain cardiac murmurs are present normally in a large proportion of healthy young people.

3. That the commoner forms of these murmurs are: (*a*) The basic systolic murmurs heard best in the third left interspace and often all over the area in the recumbent posture, and disappearing on full inspiration. (*b*) The systolic murmurs sometimes limited to the apex, sometimes heard all over the cardiac area in the recumbent posture—disappearing in the erect posture. (*c*) The cardio-respiratory, inspiratory murmurs.

4. That the truly functional murmurs—those heard in healthy individuals—should be carefully distinguished from those other murmurs which may arise at various orifices without actual valvular disease, but nevertheless, as a result of pathological changes in the heart muscles or in the blood—*i. e.*, the anæmic murmurs, the murmurs, systolic and diastolic, dependent upon weakness of the heart muscle.

5. That a familiarity with the cardiac murmurs common in the normal individual is at least as important as an acquaintance with those murmurs which are associated with cardiac disease.

DISCUSSION.

Dr. Henry Sewall: This subject has interested me greatly for some years because I have been convinced that the pathological signs are the manifestations of more or less physiological overstrain of the heart and are of practical value in throwing light on the vital constitution of the organ and in leading to prophylactic hygiene. Some years ago I called attention to the great frequency of the occurrence of a reduplication of the first sound of the normal heart when the subject was examined sitting, the reduplication disappearing and becoming replaced by a soft systolic murmur at the apex when the recumbent position was assumed. I have lately been impressed with the view that these "physiological" reduplications and murmurs find their common cause in variation of the period of closure of the auriculo-ventricular valves. Should these valves close at the end of the common diastole, the succeeding auricular systole must force the blood through them under conditions simulating auriculo-ventricular stenosis and generate a more or less marked presystolic murmur.

Again, it is easy to imagine the valves to float in such a manner that the sharply recurrent stream from the auricle will snap them shut with an audible click and give rise to reduplication of the first sound; it may be noted that the reduplicated element is nearly always obviously pre-ventricular.

In the recumbent position the hydrostatic conditions are greatly modified and the theory demands a later closure of the valves, and hence a momentary insufficiency and consequent murmur at the beginning of ventricular contraction.

The brilliant studies of Dr. Thayer on the third heart sound, and its relation to the "h" wave of the venous pulse, seem to me to strongly support the view put forward.

THE DIFFERENCE BETWEEN SYSTOLIC PRESSURE IN THE ARM AND IN THE LEG IN AORTIC REGURGITATION.

By H. A. HARE, M.D.,
PHILADELPHIA.

The sphygmomanometer has done much within the last few years to increase our knowledge of blood pressure, and gives us, when properly used, valuable facts in the fields of prognosis, diagnosis, and treatment. I desire in this brief note to call attention to the observations of Leonard Hill to the effect that in aortic regurgitation there is a remarkable difference in systolic pressure found in the arm and leg, the pressure in the lower limb being often extraordinarily high, not rarely amounting to 100 millimeters of mercury above that of the upper extremity. The results which I have obtained in making comparative studies of the blood pressure in the arm and leg of cases of aortic regurgitation have not only confirmed Hill's conclusions, but have given me even greater variations than he records, and I am prepared to agree with him that this extraordinary difference between the systolic pressure in the arm and leg is a pathognomonic sign of aortic incompetence, as it is not present in other valvular lesions.

Hill's paper, which was published in the first issue of the new periodical called *Heart*, first discusses the difference in the systolic pressure in the arm and leg in health. He finds, as have all other investigators in this field, that the difference in health is not great provided the patient is recumbent, so that the arm and the leg are on about the same level, a large part of the difference in the arm and leg being due to gravity. In other words, the systolic pressure in the leg and in the arm is practically the same, provided the patient

is perfectly horizontal and at rest for some time before the examination, the variation rarely exceeding from 10 to 15 millimeters.

One of Hill's assistants, who was carrying out observations upon blood pressure under his suggestion, reported to him that in some cases of aortic regurgitation this normal ratio did not exist, and Hill soon found that his assistant's observation was correct. Thus, he speaks of one instance in which the systolic pressure, in a case of aortic regurgitation, in the arm was 130, but in the leg 195. In another case it was 150 as compared to 200. In a third case, 160 to 240; and in still another the pressure in the arm was 106 and in the leg 156. Three other cases gave a ratio of 118 to 172; 130 as to 220; and 130 as to 180. In my own cases the systolic pressure was taken by three instruments—the Tycos, Stanton's modification of the Riva-Rocci instrument, and the new and interesting instrument of Pachon. In some tests the Tycos instrument could not be employed, as its highest register is 260. As will appear below, one of these cases showed a pressure in the leg far in excess of this figure.

In one of my cases this method of reaching a diagnosis of aortic regurgitation proved most helpful because the ordinary characteristic symptoms of this disease were not well marked. The pulse was somewhat trip-hammer in character, but not sufficiently so to be typical. Auscultation revealed a double murmur, very feeble in character, and equally well heard in the mitral and aortic areas. There was a systolic murmur transmitted into the carotid, but the diastolic murmur could not be separated from that of mitral stenosis or Flint's murmur. In this case it was found that the systolic pressure in the arms was 160 and in the legs 260. On taking the patient where there was a good light, Quincke's capillary pulse was found in the skin and in the lips.

In another case the arm pressure was 170; the leg pressure, 265.

The following tables give the results from the examination of three cases of aortic regurgitation and from several others representing various types of disease—circulatory or otherwise, but without aortic lesions. It will be noted that there is practically no difference in the blood pressure in the arm and leg except in the cases of aortic regurgitation:

Aortic Regurgitation.

Right arm, systolic, 170 mm. of Hg.
Right arm, diastolic, 135 mm. of Hg.
Right leg, systolic, 265 mm. of Hg.
Right leg, diastolic, 220 mm. of Hg.
(Taken with a Stanton instrument.)

Aortic Regurgitation.

Right arm, systolic, 160
Right leg, systolic, 260.
(Taken with a Stanton instrument.)

Aortic Regurgitation.

Right arm, 140 mm. of Hg.
Right leg, 200 mm. of Hg.
(Taken with a Tycos instrument.)

Mitral Regurgitation.

Right arm, systolic, 130 mm. of Hg.
Right arm, diastolic, 95 mm. of Hg.
Right leg, systolic, 155 mm. of Hg.
Right leg, diastolic, 120 mm. of Hg.
(Taken with a Stanton instrument.)

Mitral Stenosis.

Left arm, 130 mm. of Hg., systolic.
Left leg, 240 mm. of Hg., systolic.
(Taken with a Tycos instrument.)

Enlarged Mediastinal Glands.

Left arm, systolic, 165.
Right leg, systolic, 165.
(Taken with a Stanton instrument.)

Pulmonary Tuberculosis.

Left arm, systolic, 130.
Left leg, systolic, 140.
(Taken with a Stanton instrument.)

Convalescent Croupous Pneumonia.

Right arm, systolic, 130 mm. of Hg.
Right leg, systolic, 140 mm. of Hg.
(Taken with a Tycos instrument.)

Convalescent Croupous Pneumonia.

Right arm, systolic, 110 mm. of Hg.
Right leg, systolic, 115 mm. of Hg.
(Taken with a Tycos instrument.)

Convalescent Croupous Pneumonia.

Right arm, systolic, 138 mm. of Hg.
Right leg, systolic, 155 mm. of Hg.
(Taken with a Tycos instrument.)

The explanation of the remarkable variation between the systolic pressure in the arm and in the leg in aortic regurgitation is by no means easy. Hill believes that the great systolic wave of aortic regurgitation is better conducted by the leg arteries, and that these vessels are maintained in a contracted state to secure an adequate supply of blood to the brain. If this theory is true, nature, in endeavoring to supply the brain with blood, devises a plan whereby a far greater strain is placed upon the incompetent aortic valves.

Hill also found that violent exercise may produce a condition of high pressure in the lower extremity somewhat similar to that found in aortic disease. He caused young men free from cardiovascular lesions to run up and down stairs. In one instance the arm pressure after this exercise was 168, whereas in the leg it was 240. It is evident, therefore, that when these comparative studies are made for diagnostic purposes the patient should have been at rest for some time.

Another interesting observation made by Hill is that the high systolic pressure of the legs in aortic incompetence can be removed by immersing the legs in hot water. Thus, in one patient, the arm pressure was 110, the leg pressure 170. But after the foot was immersed the arm pressure was still 110, but the leg pressure only 140. After the foot had been allowed to become cool, the original ratio of 110 to 170 was restored. In still another case the arm pressure was 122, the leg pressure 208; but after immersion in hot water the ratio was 120 to 152. The leg was then cooled artificially, and the ratio became 120 to 172, and later 120 to 190.

If Hill's theory, to the effect that the high pressure in the legs is designed by nature to supply the brain with blood, is correct, the rapid lowering of pressure in the legs by immersing them in hot water when the patient is sitting up should theoretically produce faintness or actual syncope. Hill does not state that this accident occurred in the course of his experiments. It occurred to me that this supposititious danger could be avoided and the same relaxation of the bloodvessels in the lower limbs produced by having the patient remain in bed, wrapping his legs in a hot pack, since under these circumstances there will be less tendency to disorder of the circulation at the base of the brain. The results obtained by me under these circumstances are as follows:

CASE I.

Pressure in the right arm, 200.
Pressure in the right leg, 290.

During the pack:
Pressure in the right arm, 190.
Pressure in the right leg, 220.
A decrease of 70 millimeters in the leg.

After the pack:
Pressure in the right arm, 190.
Pressure in the right leg, 275.
A rise of 55 points in the leg.

In another case the

Pressure in the right arm was 150.
Pressure in the right leg was 255.

During the pack:
Pressure in the right arm was 150.
Pressure in the right leg was 230.
A drop of 25 points in the leg.

After cold had been applied to the legs in this case, in place of the hot pack, the pressure in the right arm was 150 and in the right leg 235. A few minutes later the leg pressure rose to 240.

The same experiment repeated in one of these cases with the Pachon apparatus gave the following results:

In the right arm the pressure was 275; in the right leg, 350 plus; how much more I could not tell. During the pack the arm pressure fell to 245, but the leg pressure remained at 350 plus.

The extraordinary degree of pressure in the lower extremity was so great that even the Pachon apparatus could not register all of it. It was because the pressure was so great that neither the Tycos nor the Stanton instruments could be employed.

In another case tested with the Pachon apparatus the pressure in the left arm was 175; the left leg, 240. During the pack the pressure in the arm was 170; in the left leg, 200—a fall of 40 points. After the pack the arm pressure was 170; the leg pressure, 210—a condition which was maintained after the leg had been chilled by cold applications.

The following results were obtained in a case of aortic regurgitation on giving amyl nitrite. Before the use of the drug the pressure in the right arm was 160; in the right leg, 245. During the effect of the nitrite it was 135 in the arm and 190 in the leg.

In a case of aortic regurgitation with aneurysm of the aorta, occurring in a woman aged about fifty-six years, the following results were obtained:

Right arm, 110; right leg, 220; left arm, 150; left leg, 195. The next day the right arm was 120; right leg, 210; left arm, 155; left leg, 200. The day following the right arm was 110; right leg, 190; left arm, 135; left leg, 210. The fourth day the right arm was 95; right leg, 185; left arm, 130; left leg, 220. The last two days the patient was under fairly full doses of nitrite of sodium.

It is interesting to note that the pressure in the right arm was always lower than the pressure in the left arm; but this is not true of the pressure in the right leg. Before the nitrite was given the pressure in the right leg was 220. After it had been taken for two days it was only 185 in this leg. On the other hand, before the nitrite was used the pressure in the left leg was 195; but after nitrite had been used it was 220. In other words, the maximum systolic pressure in the right leg before nitrite was present in the left leg after nitrite.

It would seem that these results as to the difference in pressure in the arms and legs in aortic regurgitation are not only of diagnostic value but of therapeutic usefulness as well. In a case of aortic regurgitation there are two important points to be considered. If the peripheral vessels are relaxed, particularly those in the lower part of the body, the vital centres may fail from lack of blood supply, in that the heart is unable to maintain a cerebral circulation because, with incompetent aortic valves on the one hand and relaxed arterioles on the other, normal cerebral pressure cannot be maintained. On the other hand, if the vessels in the legs are contracted to the great degree that these experiments seem to indicate, the strain on the aortic valves must be enormous and the quantity of blood which regurgitates must be greatly increased. Given a case of aortic regurgitation with ruptured compensation, it would seem unwise to use the hot footbath of Hill, but it would probably be safe to use the hot pack with the patient in the recumbent posture, since under these circumstances the brain would still receive enough blood, yet the resistance offered to the action of the heart by the previously contracted leg vessels would be diminished.

It is interesting in this connection to note that the patient who had so high a pressure as 350 millimeters in the leg soon found that a nitrite of amyl pearl would give him immediate relief if he was seized with cardiac pain during the night. A hypodermic injection of nitroglycerin was also efficacious. If nature designs the high pressure to supply the brain with blood, the use of the nitrite ought theoretically to relieve the cardiac strain but produce cerebral anemia, which it does not do. So, too, if there is a demand on the part of the brain for more blood, the average case of aortic regurgitation should be more comfortable lying prone than when propped up in bed, yet the latter position is the one which is universally resorted to by these patients.

It would seem, therefore, that these observations provide a useful means of diagnosis, but Hill's hypothetical explanation of the phenomenon does not strike me as being adequate.

THE EPIDEMIOLOGY OF POLIOMYELITIS.

By JOSEPH COLLINS, M.D.,
NEW YORK.

Half a century has elapsed since Heine published the first known description of the disease which is now commonly called anterior poliomyelitis, or, as he designated it, spinal infantile paralysis. Half a century is an extremely short time for a disease so hideous and uncompromising to hide the secret of its being; it might have done so much for longer had it not been for the ghastly epidemic of the disease that occurred in New York in 1907, which permitted Flexner to make experiments out of which has flown his brilliant discovery of its cause.

Poliomyelitis has prevailed epidemically in many parts of the world during the past twenty-five years. The great epidemics have been those that occurred in Norway in 1887 and 1895, described by Medin; by Caverly in Rutland, Vt., in 1894; by Ham in Queensland in 1904; by Geirsvold in Northern Norway in 1905, and Wickman in Southern Norway in the same year; by Zappert in Vienna in 1908; by Manning in Wisconsin in 1908; by Rekzeh, of Rheinish Westphalia, in 1909; by Shidler, of Nebraska, in 1910, and by the Collective Investigation Committee of the New York Epidemic of 1907, published in New York in 1910.

In 1908 Holt and Bartlett[1] collected the literature of thirty-five epidemics which had occurred prior to the year 1907. Since that time about twenty epidemics, large and small, have been reported, and the references to the literature of these latter epidemics are appended to this article. The literature of the early epidemics will be found appended to the article of Holt and Bartlett.

In the first epidemic reported by Medin there were forty-three

[1] Amer. Jour. Med. Sci., vol. lxxxv, p. 647.

cases and in the second twenty. In the epidemic reported by Caverly there were one hundred and twenty-six cases; in that of Zappert, two hundred and eight cases; Ham, one hundred and eight cases; Geirsvold, four hundred and thirty-seven cases; Wickman, one thousand and thirty-one cases; Zappert, two hundred and sixty-six; Manning, three hundred and fifty-two; Rekzeh, five hundred; Shidler, two hundred; and the New York epidemic, two thousand five hundred cases. The large number of cases in the recent epidemic indicate that many cases formerly diagnosticated as grippe, rheumatism, neuritis, bulbar paralysis, etc., are now recognized to be clinical forms of the disease. It is the signal service of Wickman to have pointed out the various clinical forms under which the disease may display itself.

The most remarkable secular mutation of poliomyelitis is that it is apparently a new disease. So far nothing has been found in the literature antedating 1843 which indicates that the disease existed. (In that year Colmer published in the *American Journal of Medical Sciences* the report of a case of infantile hemiplegia that he had seen in West Feliciana, Louisiana, and brief mention of ten other cases of various forms of paralysis occurring in children which was probably dependent upon poliomyelitis.) It is worthy of remark that cerebrospinal meningitis escaped recognition up to the year 1834.

The unheralded advent of a disease of which no trace has been met in history is not uncommon. The English sweating sickness made its appearance abruptly in 1486, and disappeared with equal abruptness in 1551.

Because of the short time that we have been familiar with epidemic poliomyelitis we are unable to say whether or not it is subject to the alternating periods of quiescence and recrudescence that are so common in other epidemic diseases. In this country it has not prevailed epidemically twice in the same place, unless the mild epidemic of 1909 in that portion of Brooklyn known as East New York may be so considered, nor can we say that it displays conspicuous multi-annual mutations, to use Ransome's designation for fluctuations in prevalence and virulence extending over periods of from ten to fifty years. Poliomyelitis may be constantly more or

less existent in a densely populated large city such as New York, but its existence is known only to individuals who may come in contact with it. When the disease shall be put upon the list of reportable diseases, as it is bound to be soon, then it can be determined what its multi-annual fluctuations are. One fact that is worthy of attention is that during the epidemic of 1907 in New York the death rate from other epidemic diseases was lower than it usually is. This is a fact that has often been noted in other epidemic diseases. For instance, when scarlet fever prevails, the death rate of measles is apt to be low, and vice versa.

The most remarkable thing in the epidemicity of poliomyelitis is its seasonal occurrence. It occurs as invariably in the summer months as smallpox does in the winter months, and the advent of cold weather seems to terminate epidemics in every instance. One may readily draw the inference from this that cold is inimical to the saprophytic growth of the non-obligatory parasite. In several instances it has been noted that the summers have been particularly dry. The only exception to this is a small epidemic reported by Litchfield, of Sidney, who notes that the summer was rather wetter and cooler than usual, and one in San Francisco in May and June, 1901, reported by Woods,[1] in which there were fifty-five cases.

The next most interesting feature of epidemic poliomyelitis is its communicability. Up until very recently it has been a matter of personal opinion whether or not the disease is communicable or not. Those who have reported epidemics have expressed their conviction that the disease was probably contagious, and such occurrences as that reported by Pasteur, in which seven cases occurred in one family,[2] J. M. Taylor,[3] Neumark,[4] Geirsvold,[5] seemed to leave no doubt of the contagiousness of the disease. The description of an extensive epidemic in Stockholm in the summer of 1899, in which in three different houses two cases of the disease occurred, and in several families two or three cases were observed among relatives, went far to corroborate this belief, and when Geirsvold was able

[1] Occidental Medical Times, vol. xvii, p. 77.
[2] Trans. Clin. Soc., 1897, p. 143.
[3] Philadelphia Med. Jour., January 28, 1898.
[4] Medical News, January 28, 1899.
[5] Norsk Mag. f. Laegevidensk., 1905, p. 1280.

to trace the disease from one village to another, and from one house to another, the contagiousness of the affection began to be realized. Since the publication by Wickman[1] of the epidemic which occurred in the summer of 1905 in Southern Norway, the contagiousness of the disease has been universally admitted. In the majority of instances some contact would be traced between one patient and another, and even the spread of the disease from one village to another could be traced by the passage of individuals from one town to the next town.

The most remarkable contribution to its contagiousness, however, has been made in our own country by Dr. George P. Shidler, of York, Nebraska. Dr. Shidler seemed somewhat in doubt whether the spinal disease which prevailed epidemically in York County in July, 1909, was poliomyelitis or cerebrospinal meningitis, but there can be no doubt that it was the former. Some of his cases are most illuminating in showing the contagiousness of the disease; for instance, a woman went with her child to the wedding of a sister in whose house a younger sister was ill with the disease; nine days after the mother with the child returned to her own home another of her children who had not been away from home came down with the disease. In an adjoining house there lived a family of six children, and all of them developed the disease; a woman who came to visit this family brought her baby; in five days it died of the disease. Soon after this quarantine was established, and the disease was checked. A number of other instances quite as striking as this one are published. Not the most important contribution to the epidemiology of the disease is the number of cases that occurred in families in which there were two or more children, all of whom acquired the disease. There were six cases in a family of six children, four cases in a family of six, four cases in a family of five, four cases in a family of four.

The next most important fact obtainable from a study of these epidemics is that the mortality rate varies very decidedly in different epidemics. In some it is as low as 5 per cent., in others it is nearly 20 per cent. (The highest mortality rate ever recorded was an epi-

[1] Beiträge zur Kenntnis der Heine-Medinchen Krankheit, Berlin, 1907.

demic in Sweden in which the death rate was 46 per cent.) The former figures approximate the death rate in the New York epidemic, and the latter the epidemic in York County, Nebraska.

The most careful investigations have failed to reveal that the epidemic prevalence of the disease has anything to do with unhygienic surroundings. To be sure, in some instances it was noted that the sanitary conditions were poor, especially in some of the epidemics of Norway (Geirsvold), but in the majority of the large epidemics, such as those of Vermont, New York, Nebraska, Australia, and Westphalia, the hygienic conditions were good and in some instances excellent.

The association of poliomyelitis occurring epidemically with other diseases has been made a rather important feature by many writers, and there are in the literature a number of cases showing such association. As a matter of fact, it has no relationship to infectious diseases in the vast majority of instances. In several instances there was a great mortality among chickens (Caverly, Krause), and the latter writer made the interesting observation that the shoots of small oak trees surrounding a house in which several cases occurred were noted to be covered with white fungus. This disease of the young oak shoots had only existed for a short time. This author also observes that there was a great number of cases among breast-fed children, and a number of writers point out that disorders of the digestive organs were very uncommon. Personally, I made a close study of this question in the several hundred cases that I saw in the New York epidemic, and the conclusion that I drew was that digestive disturbances had no relation to the occurrence of the disease.

A very remarkable fact was noted by Stephens[1] that there was a recurrence or recrudescence of the disease occasionally observed in the same child. Dr. A. A. Eshner thinks that he has observed a second attack of poliomyelitis in the same patient.

The territorial distribution of some of the epidemics is noteworthy, especially the epidemic of Sweden in 1905. Although the disease was pretty generally distributed through the entire country,

[1] Intercolonial Med. Jour. of Australasia, 1908, vol. xiii.

there were well-marked foci in which the disease was prevalent to a considerable extent, or to a slight extent, and then large intermediary areas in which the disease did not exist. This has been noted in several other instances, but in the New York epidemic there certainly were not foci of the disease. The disease has no apparent relationship to density of population.

Contact with a person sick of the disease is not necessary that another person may contract it. There are numerous examples of contagion by indirect contact; that is, a person who does not have the disease carrying it from a victim of the disease to another at a distance, who then falls ill with it. This has been established by the record of several epidemics, but by none more strikingly than by those of Wickman and of Shidler.

The period of incubation may be as brief as four days, or it may be a fortnight. From a study of their publications alone, it must be accepted beyond a doubt that poliomyelitis is a contagious disease. That its contagiousness varies needs scarcely be said. In the New York epidemic, the most extensive on record, the only evidence of its contagiousness was that there were two and three cases in a few families, but the most painstaking care to detect any evidence of its communicability was unrewarded.

We need no longer conjecture whether or not the disease is contagious. The points for our consideration are, what are the spreading powers of the virus, and what are the facilities for the spread of the contagion? Spreading powers of the virus vary unquestionably with the epidemics. In some cases apparently it is impossible to make it out, and in others, such as in the Nebraska epidemic and in the Westphalia epidemic, the spreading powers of the virus were commensurated with social contact and the facilities for the spread of the contagion depend upon such contact. Now that the communicability of the disease has been established, the necessity for the strictest quarantine is obvious. The period of incubation is probably five to ten days. To make quarantine of any value, it must cover cases in which paralysis does not occur, and one of the first requisites of establishing satisfactory quarantine is a recognition of cases in which classical symptoms do not occur.

STATISTICS OF EPIDEMICS.

Year and season.	Location.	Topography and hygienic surroundings.	Number of cases.	Deaths.	More than one in family.	Author.	References.	Remarks.
1907 summer and early autumn.	Sweden.	Towns and country.	1000 in the epidemic of 1905; 50 in 1906.	159; corrected mortality, 16.7%.	Many examples.	Wickman.	Beit. zur Kenntnis Heine-Med. Krankheit, Karger, Berlin, 1907.	The most complete presentation of the subject extant.
1907 summer.	Ridgway, Pa.	Country, good.	50	4	No.	Teriberry.	Long Island Med. Jour., Dec., 1907.	The disease extended down the valley in a definite direction.
1907 summer.	Oceana Co., Mich.	.....	20	Not given	No.	Griffin.	Jour. Mich. State Soc., Feb., 1908.	
1907 summer.	Dubois, Pa.	Country and village.	100	A few.	.....	Free.	Jour. Nervous and Mental Dis., April, 1908; a brief abstract only of a a paper read before the Philadelphia Neurological Society.	Meningeal symptoms common; pigs and chickens also affected.
1907 summer.	Wisconsin: Galesville.	Rural.	22	....	.....	Jegi.	Wisconsin Medical Journal, Apr., 1909.	
1908 Aug.–Oct.	Wisconsin.	Bad sanitation and sewerage; surface wells in marsh and near privy.	352 in State 167 in Eau Clair Co.	54	.....	Manning.	Wisconsin Medical Journal, Apr., 1909.	29 cases followed direct exposure to infection; 25 cases immediately after a case in same house; 2 cases in houses where this disease prevailed three and twenty years before.
1908 summer.	Minnesota: Moose Lake Barnum, Wadena.	Rural.	.....	....	In one family of 6 children, 5 ill, 2 died, 3 recovered; another family of 5 children, 3 ill, 1 died.	Hamilton.	Wisconsin Medical Journal, Apr., 1909. Northwestern Lancet Minn., Oct., 1909.	Disease assumed type of neuritis; several cases had tonsillitis.
1908 summer.	Michigan: Flint.	Rural and village.	30	5	One family: 2 little girls within a week.	Manwaring.	Jour. Mich. State Med. Soc., Apr., '09	
1908 hot, dusty weather.	Minnesota.	Good hygienic surroundings.	.....	....	A few cases only; no isolation of any cases.	Hill.	Northwestern Lancet Minn., Sept. 1, '09.	No evidence of transmission of the disease from person to person, or through infected houses or water, or by animals, or by dirt eating (common among children eating raw vegetables direct from the garden).
1908 April to June; after dry weather	Australia: Victoria.	Densely populated districts; sanitation fair.	137	6	Majority of cases in families when 3 or 4 sleep in the same room or same bed.	Stephens.	Intercolonial Med. Jour. of Australia, Nov. 20, 1908.	No severe pain in disease; incubation period 3 to 16 days; invasion, 0 to 7 days.

1908 July–Sept.	Minnesota: Northfield.	.....	20	4	4 in one family; 3 in another family; 2 in another family.	Strang.	Jour. Minn. State Med. Assoc. and Northwestern Lancet, July 1, 1909.	
1908 June-Sept; very hot and humid.	Virginia: Salem.	Town and vicinity.	25	3	No two cases in one family, even when other children were exposed.	Wiley and Darden.	Jour. Amer. Med. Assoc., Feb. 20, '09.	Cool weather interrupted epidemic for 3 weeks; then hot wave brought on 2 new cases in August; cases had pronounced hyperesthesia and sweating.
1908 June–Sept.	Massachusetts western part	3 contiguous towns and 11 neighboring towns all on banks of streams; detached houses; no sewers in majority of houses; sanitation not good.	69	5	2 cousins in same house; 2 brothers in a family; 2 cousins in another; 2 brothers in another; 2 sisters in another.	Lovette and Emerson.	Monthly Bull. Mass. State Board of Health, July, 1909.	All cases were exposed to valley influences. No correlation to curves of temperature, rainfall, and number of cases; two to three times the number of children sick were exposed and did not become ill; 6 cases over age of 17.
1908 summer.	Westphalia: Hagen.	Not remarkable (see note).	100	Not stated; 9 autopsies.	.....	Krause.	Deutsche mediz. Woch., Oct. 21, '09.	Great mortality among chickens; also shoots of small oaks covered with white fungus.
1908 summer.	Vienna and lower Austria.	Ordinary, not bad.	266	....	.....	Zappert.	Wien. med. Woch., Nov. 13, 1909.	
1908 summer.	Schenectady, New York.	Good.	29	....	.....	Clowe.	Albany Med. Jour., vol. xix, 1908.	
1908 summer.	Marburg, Germany.	.....	50	....	.....	Romer Müller.	Münchener med. Woch., Dec. 7, '09, p. 2505; ibid., Nov. 30, 1909.	Sore throats extremely common; many examples of communicability from person to person.
1908 summer.	Lewiston, Pa.	.....	30	3	2	R. T. Barnett.	Therapeutic Gazette, Sept., 1909.	
1908 summer.	Essex, Eng.	.....	8	None.	3 and 2	Treves.	Brain, Nov., 1909.	Could not trace spread of disease.
1909 summer and autumn.	Rheinish Westphalia.	.....	500	182 in one vicinity.	.....	Rekzeh.	Med. Klinik, p. 1704, No. 45, 1909.	It followed an outbreak of acute poliomyositis.
1908 summer.	Russia.	Not remarkable.	49	....	Several instances.	Schwarz.	St. Petersburg, Med. Woch., Jan. 10, 1909.	In a village of 500 inhabitants.
1909 summer.	York County, Nebraska.	Hygienic surroundings, good to fair.	200	15 7.5%	More than 1 in family 44% occurred in families in which there were more than 2 children, all of whom acquired the disease.	Shidler.	Jour. Amer. Med. Assoc., Jan. 22, 1910.	Shows the necessity of having epidemics properly studied; perhaps the most important on record, still of little use, because reported so badly.

THE PATHOLOGY OF POLIOMYELITIS.

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The recent epidemics of anterior poliomyelitis have helped to shift the chief interest in this disease from the study of the pathology to the questions of the etiology and bacteriology of infantile spinal paralysis. Nevertheless it would be of some value to consider to what extent the advanced study of the morbid changes bears on the modern conception of the disease. Our present-day knowledge we owe largely to the studies of Wickman, of Harbitz and Scheel, of Buzzard, and of I. Strauss. The last named was able to study the autopsy findings in eight cases of the recent New York epidemic. I wish to direct especial attention to the excellent work of Strauss, which has been embodied in the report of the New York Investigating Committee. If we wish to state succinctly the pathology of infantile spinal paralysis, we might say that the disease is due to an inflammatory process involving a great part of the central nervous axis, from the cranial nuclei to the lowest portion of the cord, including the spinal ganglia, and in a few instances involving even the cortical substance. It may be described as a polio-encephalomyelitis, exhibiting its chief effect upon the anterior gray matter of the spinal cord, but it is not limited to the anterior portion; the central gray matter and the posterior horns are also affected. The studies of the recent epidemics have shown a general hyperemia of the meninges of the brain and cord; hence it is not surprising that meningeal symptoms have been so frequently noted. In the acute cases the gray matter of the cord appears brownish red; from the inflammatory process in the pia we find a mononuclear infiltration of the cord. In the substance of the cord

this mononuclear infiltration is found in the interstices of the connective-tissue framework. The infiltration is either diffuse or located around the vessels, or massed in groups. This infiltration is best marked in the sacral and lumbar segments, and next in the cervical. The bloodvessels evidently play a most important role. It is chiefly but not exclusively the anterior spinal artery; the vessels of the posterior half of the cross-section and even of the lateral portions of the cord show a distinct involvement. The changes in the ganglion cells are secondary to those changes in the bloodvessels; the disease is therefore of the order of interstitial, and not a parenchymatous inflammation; at least, not primarily. The ganglion cells are found in various stages of degeneration. It is worth noting that the ganglion cells may be seen surrounded by small round infiltrating cells or polymorphonuclear cells; in some instances they have entered the cells, thus representing a true neuronophagia. The ganglion cells do not disappear group by group, but the cells that disappear are in areas in which there is a marked interstitial change. The cells of the column of Clarke were found degenerated in two cases reported by Strauss.

In five of seven cases examined by Strauss the spinal ganglia showed the same evidences of an inflammatory process, and the changes are similar to the findings in rabies. Entirely similar changes were found in the cords of monkeys to whom the disease had been communicated. The pathological findings are in entire agreement with the infective character of the entire morbid process. It may not be out of place to point out that the changes in other organs also point to a general infective process. In the lungs areas of bronchopneumonia have been found; in the liver and kidneys a parenchymatous degeneration has been made out. The spleen is invariably congested and firm and generally enlarged. In one case there was a general enlargement of the glands of the body, and in two cases petechiæ were present in the skin.

THE CONTRIBUTION OF EXPERIMENTAL TO HUMAN POLIOMYELITIS.[1]

By SIMON FLEXNER, M.D.

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Epidemic poliomyelitis has within three years become a common and widely distributed disease in the United States. Prior to 1907 the epidemic disease occurred but rarely in this country. Since 1907 it has prevailed from the Atlantic to the Pacific Ocean, and probably few States have entirely escaped its ravages. Judging from the fragmentary reports which have come to my attention, it would seem as though the Southern States had escaped wholly or in large part, but this apparent discrepancy may result from failure either to recognize the nature of the epidemic disease or to report upon it, or may be due simply to the circumstance that the fact of its occurrence in the South has not chanced to come to my attention. It is significant in respect to this point that within the period mentioned epidemic poliomyelitis has prevailed in Cuba. Before 1907 epidemic poliomyelitis had been becoming more frequent in northern Europe, and particularly, so far as reports indicate, in Scandinavia. Beginning in 1907 or thereabout a pandemic of the disease arose. The United States, Austria, Germany, and latterly France have certainly participated in the epidemic outbreaks. Whether still other countries have been similarly visited I cannot say, but it is highly probable that they have.

It is a matter of significance that the original foci of the epidemic disease in the United States, occurring in the summer of 1907, were

[1] Based on remarks made at the meeting of the Association of American Physicians, Washington, D. C., May 1910.

along the Atlantic seaboard, and that the two centres of population most seriously affected were in and about Greater New York and Boston. The particular point of importance in this regard arises from the fact that those two centres of population receive first and in the most concentrated way the immigrant population from northern and eastern Europe. Since, moreover, the best established endemic focus of epidemic poliomyelitis recorded in the last decade or two has been the countries of Scandinavia, the further fact becomes significant that the second large isolated outbreak of the disease in this country occurred in that part of the middle West, namely, about Minnesota, which receives a large influx of immigrant population from Norway and Sweden. The studies especially devoted to the question of the mode of spread of poliomyelitis which have been conducted with unusual energy and perspicacity in the last few years would seem to have rendered contagion highly probable. If the views respecting the manner of the transfer of the contagion put forward with good reason should become established, the explanation of the extension of the epidemic centres of poliomyelitis from northern Europe to America will have become obvious. The data collected in Scandinavia indicates that the contagion can be carried by intermediate persons from the stricken to the healthy, and from patients not frankly paralyzed, but suffering with slight or so-called abortive attacks of the disease. Moreover, the incubation period of the disease would appear to vary within considerable limits, being sometimes not more than two or three or four days in length, and at other times as much as twenty days, the average being eight or ten days, and thus affording opportunity for the transportation across the Atlantic Ocean of the incipiently infected. This particular problem would receive considerable illumination from facts which are ascertainable, namely, such as the number approximately of recently arrived immigrants who developed poliomyelitis in this country since 1907. I am not aware that any effort has been made in the course of the several recent extensive investigations of the epidemiology of the affection to elucidate this important point.

The idea of a contagion in respect to epidemic poliomyelitis is not a new one, but appeared in the literature more than a quarter of a century ago, and of late has been frequently invoked. The

clinical course of the disease indicated an infectious origin, but up to very recent times no convincing knowledge concerning the nature of the agent causing epidemic poliomyelitis existed. Various bacteria and especially certain cocci have from time to time been isolated in cultures from fluids obtained by lumbar puncture from patients suffering from the epidemic disease, or from specimens of the central nervous system removed from victims at autopsy. These bacteria did not conform to one species or group of microörganisms, and did not suffice to set up poliomyelitis in animals. They can be accounted for more satisfactorily as contaminations or secondarily invading bacteria than as the cause of the disease. The epidemic of 1909 in this country, in France, and in Germany led to a renewed study of the nature of the infection, in the course of which the more subtle and recent methods of bacteriology were employed. These methods led to the discovery almost simultaneously in the United States by Dr. Lewis and myself, and in France by Landsteiner and Levaditi that the infectious agent was an extremely minute microörganism that readily passed through the pores of earthenware filters, and constituted, therefore, an example of the so-called filterable viruses, of which at the present time several examples are known to cause severe diseases in man and the lower animals. The filterable nature of the virus has now been confirmed wherever the subject has been accurately investigated. Upon the acquisition of the fact of the nature of this virus, and of the further fact, upon which the discovery of the nature of the virus actually depends, that both the higher and lower monkeys are subject to the experimental disease, rest the recent great advances which have been made in the investigation of epidemic poliomyelitis.

It was predictable that the effort would be made as soon as circumstances favored to transmit poliomyelitis to monkeys. Since the disease appeared not to be transferable to the more common species of warm-blooded animals, usually available in laboratories, it became imperative to attempt its transfer to other species more nearly related to man. The last few years had, indeed, afforded several brilliant instances in which progress in determining the nature or the conquest of important infectious diseases had resulted from the use of apes and monkeys. Two examples illustrative of

this statement are afforded by syphillis and epidemic cerebrospinal meningitis. Hence, in 1907, when the first epidemic appeared in New York and vicinity, we endeavored to transfer poliomyelitis from human beings to monkeys. Unfortunately, we were at this time limited merely to fluids obtained by lumbar puncture from cases at different stages of the disease. I say unfortunately for the reason that we had the idea originally of bringing the supposed infected material directly into relation with the nervous systems of monkeys. This we, indeed, did with the fluids obtained by lumbar puncture, from which we failed entirely to produce any symptoms that we could discover, including paralysis. During the epidemic of 1907 we did not secure organs from a case of pure infantile paralysis, and we failed therefore in our intention to inoculate monkeys from the spinal cord. Had we secured such material, the discovery of the nature of epidemic poliomyelitis would, it is fair to assume, have been made two years earlier than it was. It was not until September, 1909, that we secured the spinal cord from two cases of infantile paralysis in human beings, which specimens were employed for the inoculation of monkeys by direct injection of an emulsion into the brain through a trephine opening. The first inoculations were successful. The animals immediately after their recovery from the ether anesthesia were lively and normal. They remained apparently in perfect health for a number of days, when paralysis set in. The spinal cord derived from these animals was and is still being employed to transmit the infection to still other monkeys.

During the summer of 1909 Landsteiner and Popper published an account of a successful inoculation of two monkeys with the spinal cord derived from a case of infantile paralysis in a child. They employed the peritoneal cavity as the site of injection, which led to the development of paralysis, but in endeavoring to continue the transfer of the virus by intraperitoneal injection of other monkeys, they failed entirely. Strauss and Huntoon in this country, who repeated in the late summer or early autumn of 1909 the experiments of Landsteiner and Popper, met with the same interruption of their work. Using the peritoneum as the avenue of the entrance of the virus, they succeeded in producing paralysis in a monkey inoculated with the human cord, but failed to produce paralysis when they

transferred to other monkeys a suspension of the spinal cord of the paralyzed monkey. In view of these experiments and of still other similar ones made by different investigators, it is probable that the virus contained within the human cord is on the whole more active when implanted in the monkey than is the virus contained within the monkey's spinal cord that is derived by proliferation immediately from the virus of human source. The question for the moment remains open whether this disparity depends upon the quality of the virus or the number or state of concentration of the organisms. Later studies, to which reference will be made, indicate that the virus of poliomyelitis is subject to qualitative variations, from which it follows that the sudden change of host might tend to a reduction in the potency of the virus, the fact of which reduction is exhibited when the virus is compelled to traverse a considerable territory and to overcome certain natural obstacles before it reaches the central nervous system upon which it becomes implanted. The fact of this qualitative change is far less apparent when the altered virus is brought immediately into relation with the tissues of the nervous system.

In noting the clinical effects of the inoculations we have paid attention to a number of conditions and signs that had already been indicated by observations made on the human affection. We have, therefore, observed an incubation period represented by the interval elapsing between the time of inoculation and the appearance of the first definite paralysis, which incubation period includes certain manifestations which have been noted as prodromal symptoms. Thus, the shortest period noted as elapsing between the inoculation and the onset of paralysis has been three or four days, and the longest period thirty-three days, the average period being eight or nine days. The prodromal symptoms consist of a state of undue nervousness and excitability on the part of the inoculated monkeys, or inability to fix the gaze, with which is associated a wrinkled and mobile rather than smooth and placid cast of countenance, and an erection of the hairs over the body. These symptoms are most marked for a period of from six to eight hours before the onset of the paralysis. We have not noted any constant elevation of temperature or gastro-intestinal disturbance. The onset of paralysis either when the pro-

dromal symptoms have occurred, or when they have been absent or undetected, tends to be sudden. The paralysis affecting any of the larger groups of voluntary muscles tends to be accompanied with other weak or partially paralyzed groups of muscles. In certain animals the medulla was first affected, and in them death sometimes occurred before the development of actual paralysis. In respect to location, the lower and upper extremities were affected oftener than the muscles of the trunk, and the spinal paralyses were much more frequent than the cerebral. Sensory disturbances occurred, but their investigation was much less satisfactory than the investigation of the motor disturbances. In other words, there is a striking similarity between the frank examples of epidemic poliomyelitis, whether occurring spontaneously in man or produced experimentally in monkeys. A further correspondence exists in this: Slight and evanescent or abortive attacks of the disease have been described in human beings, cases the nature of which would not be suspected were it not for the fact that they occur during the prevalence of epidemics of frank paralysis, and similar abortive or evanescent attacks have been noted among inoculated monkeys, but rarely. There is, however, one important point in which the experimental disease happily differs from the human affection. The mortality in the human affection rarely exceeds 10 per cent. of those frankly attacked, and frequently it is much less than that. The experimental disease, on the other hand, has terminated fatally in about one-half of the first series of animals inoculated, and in a much larger proportion of the later ones. Hence the experimental disease is more highly fatal than the spontaneous disease.

A still further correspondence between the spontaneous and experimental diseases is found in respect to the pathological changes or lesions. The gross lesions visible to the naked eye present in the spinal cord and medulla of monkeys consist of congestion and hemorrhage into the gray matter, chiefly, but not exclusively, confined to the anterior horns. On the other hand, the general appearances of the spinal cord, medulla, and brain are not greatly altered, and the visible effects are no proper measure of the damage inflicted by the virus.

The microscopic lesions are more severe and widespread in the

spinal cord than in the brain, and more pronounced in the gray matter and membranes of the cord than in the white matter. No part of the spinal cord, including the medulla, is entirely free from lesions, but the severest lesions tend to occur at the levels corresponding to the groups of muscles most severely paralyzed. The meninges show more or less diffuse infiltration with round cells, the greatest accumulations of which are about the bloodvessels, where thick collars of cells often exist. The infiltration is within the adventitial coat, while the muscular coat and the intima remain intact, although the lumina of the vessels are often encroached upon through compression. When the vessels are small, the effects on the lumina, and hence upon the permeability, are considerable. Meningeal cellular invasion is always interstitial, and does not give rise to exudate upon the surface of the cord or brain, and it is moreover made up almost exclusively of mononuclear cells.

The gray matter of the cords shows lesions of the anterior and posterior horns and the commissure, but the anterior horns are, as a rule, more severely and widely injured than the posterior horns. The chief lesions surround the vessels and consist of a cellular infiltration and œdema of the perivascular spaces and sometimes of hemorrhages as well. When the nerve cells and ground substance are injured, as is frequently the case, foci of similar cells occur there and the nerve cells show degeneration and necrosis. The extent of the lesions in the gray matter varies greatly. Sometimes minute foci of injury and sometimes complete degeneration of the anterior horns occur. The infiltration of the perivascular sheaths of the vessels is continuous with that of the pia-arachnoid. The white matter of the cord holds in respect to the frequency and severity of the affection an inferior position, and the lesions when present there consist of oedema, peri-vascular cellular infiltration, hemorrhage and necrosis of tissue. The brain shows lesions that are, however, more sparse than in the spinal cord. They correspond with cellular infiltrations of the meninges similar to but less in amount than in the cord. The intervertebral ganglia regularly are the seat of a diffuse and nodular infiltration with lymphocytic cells, which collect between the nerve cells and about the nerve fibers, both of which may be the seat of degeneration or of necrosis.

The pathogenesis of the affection is explained by the nature and distribution of the lesions. It would appear that the virus becomes implanted upon the leptomeninges, especially in the region of the spinal cord and medulla, where it sets up cellular infiltrative changes that are most marked in the perivascular lymph spaces of the arteries entering the nervous tissues. The vascular lesions constitute the primary causes of the lesions of the nervous tissues, the severity of which is determined by the particular vessels affected and the intensity of the involvement. The infiltrative lesions are confined to the perivascular lymph sheath and adventitia, but still other lesions must occur in the intima of the vessels from which the œdema and hemorrhage arise. The central arteries entering the anterior median fissure and supplying the anterior gray matter of the cord invariably become affected, through which the preponderance of lesions of the anterior horns is accounted for. Since the arteries supplying the posterior gray matter are less important, the lesions in the posterior cornua are slighter. The degree, therefore, of affection is determined by the richness of the arterial blood supply, whence is explained the liability of the lumbar and cervical enlargements to severe lesions. Irregularity in the branching of the central artery probably explains the common variations observed in the involvement of the two lateral halves of the body. The brain is far less commonly the seat of lesions, but it is not spared. Paralysis of the cranial nerves and especially of the facial nerve follows upon them, but lesions also occur in parts of the brain which do not respond by paralysis. The brain injuries, like those of the cord depend upon vascular lesions.

Hence it would appear that there are good grounds for believing that a considerable part of the paralyses, especially those that are not permanent, are the effects of temporary vascular impediments. The impediments are all outside the lumina of the vessels, which are merely reduced in caliber through pressure. Thrombi do not occur. Some of the functional disturbances are possibly thus anemic in origin, others are probably caused by slight degenerations, and still others are undoubtedly caused by focal hemorrhages and œdema. All these effects may possibly be recovered from: part by resolution of the cellular vascular infiltrate and reëstablishment of the lumina;

part by absorption of œdema and hemorrhages, and part by restoration of the mildly degenerated nerve cells. The severer degenerative and other lesions, through which actual necrosis is produced, do not become restored. Upon them depend the permanent paralyses and deformity.

The virus causing epidemic poliomyelitis has been stated to be of very minute size. It is, so far as we can now judge, one of the most minute organisms known to cause disease. This conclusion follows from the fact that in aqueous suspension, such as is secured through preparing an emulsion of the spinal cord in distilled water, it passes with great readiness and little or no loss of potency through the pores of the densest and finest porcelain filters, namely the so-called Chamberland filter. It passes with even greater ease through the somewhat less dense Berkefeldt filter. It is extremely doubtful whether the virus has actually been seen. On staining film preparations of the filtrate with mordanting dyes, preparations are secured which under the highest powers of the microscope exhibit minute points, circular or slightly oval in form, which possibly, although not certaintly, represent the stained parasite. When the filtrates are examined under the dark field microscope, innumerable bright dancing points, devoid of definite size and form, and not truly motile, can be discerned. That these particles represent the microörganisms of poliomyelitis cannot be affirmed, since similar particles are present in filtrates obtained from nervous and other tissue which can be viewed also as consisting of simple protein matter.

The filtrates are highly potent. Quantities as small as one one-thousandth to one one-hundredth of a cubic centimeter suffice to cause paralysis in monkeys after the usual incubation period, when injected into the brain. The virus is highly resistant to external agencies and conditions. It withstands glycerination for weeks or months very much as the virus of vaccinia or rabies does. It withstands drying over caustic potash for weeks without any or marked reduction in potency, showing a greater degree of resistance than the virus of rabies. It retains its virulence apparently unimpaired for weeks on being kept constantly frozen at minus 2° to 4° C. It also withstands for a long time temperatures slightly above the freezing point of water, in the course of which the nervous tissue

containing the virus undergoes autolysis; and it has been shown to survive the growth of ordinary mould. On the other hand, it is readily injured by heating, since temperatures of 45° to 50° C. maintained for half an hour suffice to render the filtrate incapable of causing paralysis. It is also readily destroyed by a 1 per cent. solution of hydrogen peroxide, and by such simple disinfectants as menthol.

That the virus is a living organism must be concluded from the fact that such minute quantities of it suffice to carry infection through an indefinite series of animals. We have propagated the virus now through twenty-five generations, representing twenty-five separate series of monkeys, and as many removes from the original human material supplying it, and the activity of the virus for the monkey has increased rather than diminished in the course and as the result of the successive transplantations. Whether the virus has been or is to be cultivated outside of the body is still an undecided question. We early secured certain indications which led us to hope that the virus multiplied in a medium of bouillon mixed with human serum. We have, however, not succeeded in producing paralysis by the inoculation of one of these possible cultivations. On the other hand, original virus has been observed to retain its virulence for several weeks when kept in a similar bouillon at the temperature of the thermostat.

At the outset of the experiments we estimated that less than one-half of the monkeys that became paralyzed would, if permitted, recover more or less completely from the paralysis. Since, however, our purpose was best served at the time by sacrificing the paralyzed animals immediately on the appearance of the paralysis, they were, as a rule, etherized. We now believe that the deduction was erroneous and that the fatalities would have been greater than we supposed and probably as many as three-fourths of the paralyzed animals would have succumbed to the disease. At this early period, however, a number of paralyzed animals recovered, usually, however, incompletely, and retaining residues of the paralysis similar to what is observed in the spontaneous human affection. The indications now are that the virus has altered qualitatively and so increased in potency in the latter generations that recoveries are hardly to be looked for.

The mortality at present approaches 100 per cent., with which figure there is happily nothing in the pathology of the human affection that is comparable. In view of certain experiments of a therapeutic character which are to be mentioned, the fact of the intense activity of the virus should be borne in mind. Undoubtedly, examples of the virus will be discovered which will become modified in the reverse direction, and lose rather than gain in activity. At one period, indeed, in the course of propagation of each of the two viruses which we originally secured, there occurred what appeared to be a sharp decrease of virulence, a change indicated by feeble effects during several passages and the final loss of power of certain strains to transmit the infection. To the circumstance that we carried the virus forward in parallel series of inoculations is to be attributed the survival and increasing activity of the strains at present in use.

Repeated attempts have been made to implant the virus upon other animals, but without success.[1] The animals thus employed consisted of the available warm-blooded domestic animals of this country, and included guinea-pigs, rabbits, rats, mice, dogs, cats, sheep, cows, goats, pigs, chickens, pigeons, and horses. The rabbits and guinea-pigs were inoculated directly with each of the two specimens of human virus, and additional rabbits and guinea-pigs and the other animals with virus derived from monkeys. In contrast with these failures is the successful employment of several species of monkeys. The greater number employed were of the species Macacus rhesus, but all other species of old world monkeys seem equally susceptible. These included, besides M. rhesus, M. cynomolgus and nemestrinus, Cercocebus fulignosus, Cercopithecus callitrichus, and Papio babuin. Of the new world monkeys we employed two species, one belonging to the genus Cebus, and the other including Capuchinus. It chanced that the larger ring-tail proved susceptible, and the smaller did not, so that a question arises whether the catarrhine are not more uniformly susceptible than the platarrhine species. No instance of the spontaneous transfer of the virus from a paralyzed to a normal monkey arose, although many

[1] Krause and Meinicke in Germany, of all those engaged in the recent investigations, alone claim to have transferred the disease to rabbits.

opportunities for contagion in the course of our many experiments occurred. This fact does not militate against the notion of contagion in respect to the spontaneous disease in man, for the reason that the monkey is obviously under ordinary conditions and because of the possession of adequate external means of defence an insusceptible species, although once these defences are surmounted it proves less able to resist the injurious effects of the virus than do human beings.

We have seen that the intracerebral mode of infection is not the only successful one, and that the virus may be introduced into the body by way of the peritoneal cavity, under circumstances leading to paralysis. It has been proved that the virus, when derived from an infected monkey, may also be introduced successfully by way not only of the peritoneum but also by means of the general blood, the subcutis, spinal canal, large nerves, and certain mucous surfaces. Thus the introduction of large quantities of virus into the stomach or duodenum does not lead to paralysis unless the motions of these organs are for a time arrested by means of opium When peristalsis has thus been prevented infection and paralysis result in some instances after this mode of introduction of the virus. However, it would appear that none of the avenues mentioned lead so uniformly to paralysis as does the direct or intracerebral mode of inoculation into the nervous tissues. There exists, however, one mucous surface that is more readily traversed by the virus than the other avenues, excepting the brain, and that is the mucosa of the nasopharynx. If this mucous membrane is lightly scarified in an etherized animal, and the virus is rubbed into the scarifications by means of a swab, infection and paralysis usually and with few exceptions result with promptitude. Our experience is to the effect that the tracheal mucosa and the lungs do not afford an easy point of entrance of the virus into the body, at least under conditions in which gross lesions of the superficial tissues have not been previously produced.

The facts just given concerning the several possible portals of entry of the virus of poliomyelitis into the body under conditions leading to paralysis have significance with respect to the usual portal of entry of the poison in the spontaneous infection in man. We have been led by certain theoretical considerations to view the

nasopharynx as the location in the body to be regarded with special suspicion as being the portal of entry of the virus. Some of these theoretical considerations may be mentioned. Our attention was arrested by the frequently observed fact that in point of distribution epidemic poliomyelitis resembles epidemic cerebrospinal meningitis, and that the two diseases, indeed, presented such close similarities in this respect that they had often been confounded with each other. The chief and striking difference between them related to the seasonal prevalence, which for epidemic poliomyelitis is midsummer, and for epidemic cerebrospinal meningitis late winter or early spring. The two diseases moreover, attack by preference infants and young children, although not sparing older children and adults, and in about the same ratio. In the majority of instances a single case appears in a family or home, but often two cases, and less often three or more cases appear. The relation between the group cases in a house or locality has in respect to both diseases been made out only recently, through the discovery of the role of the intermediate carrier of the infection.

Now it is held that the Diplococcus intracellularis passes into the cerebrospinal membranes by way of the lymphatic connections existing between them and the nasopharyngeal mucous membrane. None of the lower animals, not even monkeys, are so susceptible to the pathogenic effects of the Diplococcus intracellularis that its inoculation into the nasal mucosa suffices to set up acute meningitis. We have already seen that the virus of poliomyelitis, which is so much more active, can be introduced successfully by direct inoculation into this membrane.

The considerations thus far given show the close agreement existing between the two diseases, epidemic meningitis and epidemic poliomyelitis, in respect to the part played by the nasopharyngeal mucous membrane. Still other considerations are these: It is difficult, if not impossible, to establish in human beings the fact that the diplococcus passes from the meninges by a reverse lymph current into the nasopharynx, and yet such a migration is not only highly probable, but would most readily and satisfactorily explain the persistent intracellularis infection of these mucous membranes, which is regularly present in epidemic cerebrospinal meningitis.

The case is quite different in monkeys infected with Diplococcus intracellularis by injection of cultures into the lumbar spinal canal, in which the migration into the nasopharynx of the diplococcus contained in leukocytes and free also has been followed with the microscope. It may therefore be regarded as established that this mucous membrane serves both in the site of escape from and of entrance into the meninges of the Diplococcus intracellularis in man. The question arises: Does this membrane serve a similar double function in respect to the virus of poliomyelitis? That it may serve for its entrance into the body we have already seen, and the experiment is readily made to determine whether or not the virus is also excreted there. The excised mucosa of monkeys recently paralyzed and killed has only to be rubbed up with quartz sand suspended in distilled water and pressed through a porcelain filter in order to secure a fluid free from bacteria and suitable for inoculation into the brain of healthy monkeys. By employing this method we have been able to produce paralysis and thus to prove that the mucous membrane contains the virus. The virus in the mucous membrane is not derived from the blood contained within it. It is true that the blood does contain the virus, but in such minimal quantities that an amount of two cubic centimeters may fail to cause the infection, while as much as twenty has caused typical paralysis. Moreover, we have ascertained that the organs generally do not contain the virus in such amounts as readily to convey the infection. We have failed repeatedly to secure infection from the spleen, bone marrow, liver and different groups of lymphatic glands, and in several experiments failed to develop paralysis after injection of the salivary glands, although Levaditi has reported one such successful experiment among several failures. We have failed to produce paralysis by the injection of a suspension of the mesenteric lymph nodes taken from an animal that had become paralyzed as a result of an intrastomachic injection of the virus, while we have been successful in producing paralysis with the mesenteric lymph nodes secured from a human case of poliomyelitis. That the lymphatic glands in the monkey are capable of retaining the virus in an active state is proved by the fact that after subcutaneous inoculation of an emulsion of the spinal cord derived from a paralyzed animal

the regional lymphatic glands (axillary and inguinal) proved infectious. Again, Römer and Leiner and Wiesner have in certain instances caused paralysis by injecting into the brain emulsions of the mesenteric and of the cervical lymphatic glands taken from monkeys which became paralyzed following an intracerebral inoculation of the virus. It appears, therefore, that the virus may be retained for a time by certain distant organs, and especially by the lymphatic glands, which it reaches through the general circulation; but these localizations give no indication of the point of entrance into the body of the virus. The virus has thus far not been found in the excreta, that is, in the feces and urine, or in the intestinal mucosa or bile. Since the virus is filterable it is possible to demonstrate its presence in material highly contaminated with bacteria.

We are disposed to the view that the nasal mucosa serves not only as the portal of infection but also as the path of elimination of the virus into external nature, since such elimination must occur in order that the virus be maintained alive and transmissible. It is well known that direct connections exist between the meninges and the nasal mucosa by way of the lymphatics, which pass with the filaments of the olfactory nerve through the cribriform plate. We have already alluded to the fact that the virus first becomes implanted upon the leptomeninges, and this primary location is what would be especially favored by the mode of entrance of the virus just mentioned. That the early participation of the leptomeninges does not occur without certain definite corresponding alterations taking place in the cerebrospinal fluid we have been able to demonstrate. It will be recalled that the cerebrospinal fluid obtained by lumbar puncture from cases of the human spontaneous disease at different periods after the onset of paralysis, have shown only slight qualitative abnormalities. These fluids, which are clear, but may be in excess, show merely a moderate increase of the lymphocytes normally present, and no other qualitative changes. Moreover, this fluid has been shown by repeated tests to be non-infectious, or at least not capable of setting up paralysis in monkeys, even when injected into the brain. In monkeys, on the other hand, in which the spinal fluid can be investigated during the incubation

period of the disease as well as after the development of paralysis, it has been shown that the reaction of the meninges to the injection of the virus occurs quickly, and that at the expiration of periods of twenty-four, forty-eight, or seventy-two hours the number of cells within the fluid has progressively increased, so as to give rise to a slight opalescence of the fluid, which becomes subject also to spontaneous coagulation. The fluids contain an excess of protein, as may be shown by means of Noguchi's butyric acid test. This condition of increased cells and protein is of brief duration, and is succeeded by one in which the fluid is clear and non-coagulable, the protein not increased, but only the lymphocytes are more numerous than normally. This is the state of the fluid in monkeys at a period concurring with the onset of paralysis or appearing soon after, so that there is essential agreement between the two conditions. The spinal fluid taken from monkeys when clear and limpid, does not convey the infection and produce paralysis, but when the fluid is taken at an earlier period, at the height of the opalescence, it is capable of transmitting the disease. Finally, the question arises whether the virus of poliomyelitis can be directly implanted upon the leptomeninges, which question can be answered in the affirmative. If an active virus is introduced by lumbar puncture into the meninges, infection and paralysis may be produced. Hence it would appear as though all the theoretical conditions required to establish the nasal and meningeal route as a direct one for infection in poliomyelitis had been supplied by experiment. It remains to add that in course of the demonstration given by these experiments two important subsidiary problems have been elucidated: First, the pathogenesis of the affection has been rendered clear and comprehensible, and next the changes in the spinal fluid induced by the infection have been brought clearly into view as constituting criteria upon which, even in human cases, an early diagnosis of the disease, preceding the onset of any meningeal or paralytic symptoms, may come to be based. What is required merely is that those physicians[1] having access to clinical cases should perform lumbar puncture

[1] The earliest cellular reaction in monkeys is not lymphocytic, but includes polymorphonuclear leukocytes, which may predominate for the first period of one or two days. The earliest reaction of the meninges in human beings also is attended with polymorphonuclear excess (Wickman and Fulton).

early when poliomyelitis is suspected, and during the prevalence of an epidemic upon patients presenting a series of indefinite symptoms that precede as prodromata the onset of paralysis, or themselves comprise the group symptoms that may define the so-called abortive form of the affection.

Experiments have been conducted to determine the kinds and degrees of immunity which are produced by the inoculations of the virus of poliomyelitis. Since the literature on epidemic poliomyelitis is silent on the subject of reinfection, it can be inferred that two attacks of the disease are rarely, if ever, suffered by one individual. Two possible reasons can be assigned for this: The first and most probable is that one attack of this disease, as is the case with some other acute general infections, tends to afford an enduring immunity, and the other, that as epidemics have in the past occurred infrequently and reappeared after long intervals, the children once affected have passed beyond the susceptible age period at the time of the next epidemic.

We have available in monkeys which have recovered from an undoubted infection, attended by paralysis, an opportunity to decide the question whether an attack of poliomyelitis protects against subsequent infection. Thus far we have subjected a number of monkeys to reinoculation into the brain at periods varying from eight days to four or five months, after the paralysis first appeared, without succeeding in reinfecting any of these animals. They were not rendered perceptibly sick by the subsequent inoculation after the one originally producing paralysis, and in no instance was recrudescence of the paralysis produced. It is interesting to note that in point of severity the first attack varied between mere tremor of the head, a partial paralysis of one limb and complete paralysis of legs and arms. The paralysis had in some instances nearly or completely disappeared and in others it had become reduced, but still affected all the muscles of one or two limbs. These results indicate what will probably be found to be true equally of human beings, that an undoubted attack of poliomyelitis, even when unaccompanied by definite paralysis, produces a state of refractoriness to reinoculation with active virus that endures for months and probably for years, if not throughout the life of the affected indi-

vidual. On the other hand, our experiments, embracing now a large number of monkeys, established that when the virus is introduced into the brain, practically all monkeys belonging to the generally susceptible species are subject to infection, although they do not invariably succumb to the first inoculation, but may require a second injection. However, it would still appear that rare indiviudal monkeys are highly refractory to infection, and it has also been observed that an unsuccessful inoculation of the virus does not act as a protective, but leaves the unaffected animals either with their original degree of susceptibility unimpaired or, what further experimentation will be needed to confirm, leaves the animals possibly somewhat more disposed to a subsequent infection.

This latter point of the failure of an unsuccessful intracerebral inoculation of the virus to increase resistance does not answer the question negatively, whether by suitable means it may not be possible to develop an active immunity independently of the production of even the most trifling symptoms that might be taken to indicate an attack of poliomyelitis. We have, indeed, been successful in establishing in a certain number of monkeys a state of active immunity through a single large subcutaneous injection of the crude or modified virus, as represented by the emulsions of the spinal cord taken from recently paralyzed monkeys, or by repeated injections of gradually increased amounts of the crude virus. This mode of producing acitve immunity has not up to the present been developed into a uniformly successful and safe method, since of the treated animals some do not develop a strong immunity and others develop paralysis as a result of the treatment. The direct immunizing effect has been produced also by means of a virus somewhat modified after a long immersion in glycerin, so that it may be regarded as probable that a qualitatively modified virus, changed through the action of chemical or physical agents, or modified by biological conditions within certain hosts, can be produced, and that this altered virus will be found more appropriate than the virus of full potency for purposes of active immunization. At present the experimental basis is entirely inadequate to justify the attempt to induce active immunity as a protective measure in human beings. Monkeys thus directly immunized resist successfully the injection of large doses of virus into the brain.

It has, therefore, been established that an undoubted and even high degree of immunity to infection with the virus of poliomyelitis is obtainable in animals, and probably equally in human beings. The question which next arises is this: As a result of this immunity, do the body fluids acquire new properties capable of experimental demonstration upon which the immunity probably depends? In answer it can be stated that human beings and monkeys who have passed through an attack of poliomyelitis come to contain in their blood certain neutralizing principles for the virus of poliomyelitis, and that these principles are readily demonstrable by animal tests for two or more years in human beings, and that they probably persist for as great a period in monkeys. Similar principles are absent from the normal serum. They are demonstrated by bringing into contact an active filtrate containing the virus with the serum of the blood derived from animals or human beings who have recovered from poliomyelitis, or from monkeys actively immunized directly to the virus, and incubating the mixture for a period at 37° C., and determining that after this treatment the virus is no longer able to set up paralysis upon being injected into the brain of normal monkeys. Furthermore, it has been shown by Netter and Levaditi that the blood of a patient who had suffered an abortive attack of poliomyelitis contained such neutralizing principles.

A pressing question could now be approached, namely, whether the immunity principles contained within the serum suffice to neutralize the virus of poliomyelitis once it is present in the body. It could be assumed that the serum of animals as of human beings that had recovered from paralysis would contain the immunity principles in no high state of concentration. Effort was therefore made to reinforce the degree of immunity in these monkeys by subsequent inoculations of virus, and the therapeutic experiments defined were conducted in part with this reinforced serum, and in part with the serum of directly immunized monkeys and such serum as could be obtained from human patients. It can now be stated that if the quantity of the virus injected into the brain be not in excess of a given dose the development of paralysis can, in some cases, be prevented by making several injections of the serum by lumbar puncture into the subarachnoid space, while in another number of

animals the onset of paralysis is much delayed. In respect to the latter point it may be stated that the period of incubation in the control animals ranged from seven to eleven days, and in some of the animals treated with the human serum the onset of paralysis was delayed until the twenty-sixth or twenty-seventh day. Moreover, infection by way of the nasal mucosa can also and with greater certainty be prevented by the serum injections. The manner of making the therapeutic injections was somewhat varied, but in general may be described as follows: An intracerebral injection of the virus having been made after the expiration of a period not exceeding twenty-four hours, the subarachnoid injections of the serum were performed on three successive days, after which, an interval of three days having been allowed to elapse, three more daily injections of serum were given. We chose the subarachnoid method of injection rather than the intravenous mode, in order that the immunity principles might be brought into the most direct relationship with the virus, and particularly in view of our conception of the pathogenesis of poliomyelitis and of the primary site of localization of the virus in the leptomeninges. We believe that as good results could not be achieved by the intravenous injection of the serum, although the immunity principles could doubtless be brought to the nervous tissues by the circulating blood, for the reason that we know that these principles are not readily if at all secreted into the subarachnoid space. Hence they would not come into relationship with the seat of the active virus at a period preceding its active proliferation and extension throughout the nervous tissues. We think it also probable that had the serum injections been resumed after another interval of rest, the last vestiges of the virus in the tissues might have been destroyed in those animals in which the incubation period was much delayed, so that the ultimate appearance of paralysis might have been entirely prevented.

We have sought to ascertain whether animals protected from infection through the employment of mixtures of virus and immune sera or as a result of treatment by subarachnoid injections of immune sera for therapeutic purposes exhibited an unusual degree of resistance to subsequent intracerebral injections of active virus made at periods of several weeks to four or five months after the

conclusion of the original experiments. The object of these tests was to ascertain whether a permanent augmentation of the natural resistance to infection had been accomplished by the introduction of the virus under these conditions of restraint into the body. We have found that no unusual degree of resistance to subsequent intracerebral injections of active virus has resulted, which fact, we believe, points to the validity of the following deductions: (1) A neutralized mixture of virus and immune serum does not lead to any degree of active immunization; (2) the therapeutic action of an immune serum is associated with restraint of multiplication of the virus such as would be required to establish any grade of active immunity; (3) a simple passive immunity is either not produced at all by the serum injections, or is of brief duration or small amount.

The observations on immunity which have been presented early suggested that an effort be made to produce a corresponding active immunity in some of the lower animals that might possibly become the source of a therapeutic serum. This particular phase of our studies is being actively pursued at the present time. However, several facts have already been developed. It has, for instance, been found that the horse does not readily respond even to large injections of filtrates carrying the active virus with the development of immunity principles within the blood. It is true that our experiments are restricted for the present to a single horse, the blood serum of which, after many months of treatment, had no restraining effect on the virus either *in vitro* or within the body. The rabbit and chicken would seem not to yield such immunity principles. On the other hand we have secured indications that the sheep may react more favorably. It has been found that normal sheep serum possesses a definite although slight neutralizing power for the filtered virus when mixed directly with it, and that the injection of emulsions of the spinal cord and brain of recently paralyzed monkeys into the sheep augments this property of neutralization. What remains to be determined is the degree to which this augmentation can be carried, and whether a serum can be secured that will possess therapeutic value; but should the sheep fail in this respect, the search must be continued and made to include still other species of animals, in the hope that one will be found in which the immunity response

will be greater. There are serious objections to the use of monkeys as a source of a therapeutic serum, even were one of high potency capable of being prepared in those animals. The use of human serum, derived from persons who have passed through an attack of poliomyelitis, as a therapeutic agent, would be free of certain objections attached to the use of monkey serum, but it is not very probable that such an immune serum would be found to have sufficient strength or that it could be procured with sufficient readiness to make it available for practical application. Finally, the serum treatment of poliomyelitis must at the present time be regarded as strictly in the experimental state, and it cannot be predicted how soon or whether ever at all such a form of specific treatment of the disease will be applicable to the spontaneous epidemic disease in human beings.

It may be confidently stated that the experimental study of poliomyelitis has yielded a large number of important facts relating to the spontaneous disease in man. These facts include the discovery of the nature of the virus, of many of its properties, of certain important clinical and pathological peculiarities of the disease, of the phenomena of immunity, of a mode of spontaneous infection, while they have served to establish a basis on which to develop measures of prevention, and upon which to build hopes for the working out of a specific method of treatment. Moreover, the advance which has now been accomplished will make it possible to determine with accuracy whether poliomyelitis is a single clinical and pathological entity, or a generic name covering groups of symptoms and descriptive of the effects of certain lesions of the spinal cord and brain of which epidemic poliomyelitis is merely one, but the most important variety. It is not improbable that poliomyelitis, like meningitis, may be found to arise from several independent causes, and that epidemic poliomyelitis, like epidemic meningitis, may be distinguished among the varieties by being invariably the product of a specific microörganism. We possess already evidence to the effect that certain of the lower animals, among them poultry, the dog, and possibly the horse, are subject to poliomyelitis, due apparently, in each instance, to a cause peculiar to the species affected.

DISCUSSION.

Dr. Mark W. Richardson: The State Board of Health of Massachusetts has been making an investigation of this disease for the last three years. In 1907 the number of cases was 235. In 1908 it was 185. In 1909 the number of cases was about 1000. This increase in the number of cases is to be accounted for only in part by the increased interest in it on the part of the medical profession. Contrary to what might be expected, the disease is not found chiefly in cities, as might be inferred from the appearance of maps. For instance, although there were in Boston last year 299 cases, the city ranked sixty-fifth among the cities and towns in which this disease appeared. Furthermore, the average population of the first twenty-five cities and towns in which the disease occurred most frequently was about 3000, whereas the average population of the twenty-five cities and towns least affected was over 30,000—indeed, most of the large cities are included in this last block of twenty-five. This fact shows, apparently, that the disease is not a city disease, but rather one of rural or suburban localities.

Another interesting point is that a community severely affected one year is apt to escape the next. For instance, in 1907 there were a good many cases in the Berkshire district, whereas in 1908 there were few. In 1909 the disease appeared again in about the same proportion as in 1907. In 1910 the cases have been very few in number.

The seasonal incidence of the disease is also interesting. In this climate, it occurs chiefly between the months of May and November. Similarly, in the Southern Hemisphere, the time of greatest prevalence is from March to May. In Cuba the disease is seen, as with us, chiefly between the months of May and October, a fact which would seem to show that temperature alone is not the determining factor in the incidence of the disease.

Investigation as to the occurrence of anterior poliomyelitis in institutions in which children are kept brought out the interesting fact that out of 3600 such children, only one case of anterior poliomyelitis occurred. It would seem, therefore, that children living in such institutions are protected in some way from influences which bring about infection.

In combating the disease it has been recommended that patients be quarantined in a manner as strict as that observed in scarlet fever. The use of urotropin has been recommended also, in view of the fact that this drug has been shown to be eliminated in the cerebrospinal fluid. A considerable proportion of fatal cases have shown an enlarged thymus gland. Whether there is any important relation between these two conditions cannot be stated at the present time.

Dr. B. Sachs: In performing autopsies on these cases of acute anterior poliomyelitis, other organs besides the thymus gland may yield evidences of a general infection. The lungs, the liver, and the spleen may show distinct evidences of

such an infection. In one case of mine every single gland of the body was found to be enlarged.

Dr. Simon Flexner: It would be possible to determine the effect of urotropin in this disease by animal experimentation. Experiments that we have carried out with disinfecting agents have shown that the virus is not difficult to destroy with certain disinfecting agents that can be used therapeutically.

At autopsies the fact has been observed among children who were the victims of epidemic anterior poliomyelitis that the thymus gland is enlarged frequently.

A HISTOLOGICAL STUDY OF THE SWEAT GLANDS IN CASES OF CHRONIC NEPHRITIS.

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General Considerations. The belief that impurities might be removed from the body by means of sweating dates from ancient times. Civilized nations have shared this belief with savages. The use in all parts of the world of natural thermal baths, hot-air baths, vapor baths, and wet packs testifies to a universal faith in the skin as an organ of elimination. The standard text-books on the practice of medicine, under the heading of the treatment of nephritis, or uremia, recommend baths or other means of securing free perspiration. They usually imply, if they do not specifically state, that the work of the kidneys may be lightened through the excretion of solids by the sweat glands. Some, like von Noorden, doubt that the sweat glands excrete a sufficient amount of solids to be of value, although agreeing that the removal of water may be beneficial.

Analyses of perspiration from healthy persons show that it contains only a small amount of solids in solution. Sodium chloride predominates among these solids, which is of interest in connection with the theory that retention of chlorides in the tissues favors edema and the use of sweating to relieve edema. Persons who exercise violently may, however, excrete an appreciable amount of nitrogen in the perspiration. In the experiments of Benedict as much as 0.22 gram nitrogen was excreted per hour (equivalent to nearly 0.5 gram of urea).[1] The phenomenon of an excretion of urea by the sweat glands to the extent of coating the skin with crystalline scales is described in text-books.

[1] American Medicine, January 20, 1906.

It seemed to me that the facts just stated suggested that a study of the sweat glands in cases of chronic nephritis might be at least interesting. However, it has not been the purpose of this study to establish any relation between nephritis and such well-known diseases of the skin as eczema, which has sometimes been claimed. No cases with obvious skin disease have been considered. A further reason for examination of the sweat glands in cases of chronic nephritis has seemed to be the relation, which is quite generally admitted, between gastro-intestinal inflammations and chronic nephritis. The practice of giving saline purgatives in the hope of aiding the kidneys in nephritis seems to be universal. In explanation of these gastro-intestinal inflammations, some writers hazard the assertion that the intestine may vicariously assume the function of eliminating when the work of the kidneys is insufficient, and that the intestine may suffer in the process. By analogy, it appears not impossible that the sweat glands likewise might suffer under similar circumstances. I have made no attempt to examine the literature, but if pathological conditions of the sweat glands in cases of nephritis have been described, it is apparently, at least, not a matter of general information.[1]

Normal Histology. A few features in the normal histology of the sweat glands may be briefly reviewed. The duct, of course, begins as a spiral cleft in the epidermis, which receives an epithelial covering of its own, continuous with the deeper layers of the epidermis where it enters the true skin. The duct continues, to become the coiled portion of the gland, deep in the true skin or in the adjacent subcutaneous tissue. The structure of the duct extends into the coil for a considerable distance (about one-fourth of the length of the coil). The duct is lined with two or three layers of somewhat flattened epithelial cells, whose borders next to the lumen are differentiated into a narrow, homogeneous cuticle. The duct is surrounded by a delicate basement membrane, more delicate than that of the secreting portion of the tube. In the secreting portion of the coil the epithelial cells are cubical or columnar, one layer deep; inside of the basement membrane are a few longitudinally elongated

[1] See the recent article Sull' Anatomia Patologica delle Ghiandole Sudorifere, Demil. Patologica I, No. 2.

cells, not forming a continuous layer. They are usually regarded as muscle fibers.

The lumen of the gland or duct may contain amorphous or granular eosin-staining material, evidently precipitated or inspissated secretion. It is stated that, following active secretion, the cells of the secreting tube become shrunken. These last two points are important in estimating pathological conditions. According to Unna, the sweat glands secrete an oil or fat. The form of the coiled part of the gland is beautifully shown in the reconstructions of Huber and Adamson.[1] The average diameter of the whole coil is a little less than 0.5 mm. There is an abundant plexus of blood capillaries among the tubes.

Technique. Specimens of skin were taken in all cases from the sole of the foot close to the plantar fold, which proved to be much the most satisfactory location. In about half of the cases samples were also secured from the anterior surface of the abdomen. The sole of the foot was chosen because of its abundant supply of sweat glands, its freedom from hairs and sebaceous glands, and the possibility of securing specimens without disfiguring the body. The statements made in this paper refer to skin from the sole of the foot entirely. A few trials were made with skin from the axilla, but the pictures secured were so confusing that this region was not used further. A piece of kidney was taken in all cases. Alcohol fixation, paraffin embedding, and hematoxylin and eosin staining were found most satisfactory after trying various other methods. Sections were cut to a standard thickness of 10 μ, or, for special purposes, to 6 μ.

Pathological Histology. The cases included in the present study were 75 in number, mostly chronic interstitial nephritis; there were a few cases of large white kidneys, pyelonephritis, and tuberculosis of the kidney. The cases of chronic interstitial nephritis were of every grade, from the most trifling to the most extreme. At first, normal skin was taken for comparison from amputations of the foot from accident cases. It was soon found indispensable to know the condition of the kidney, and later, skin from autopsies only was used. The weakest point in the present work is the lack of a sufficient number of normal cases for comparison. Even from young adults,

[1] Contributions to Medical Research, dedicated to Victor C. Vaughan, 1903, p. 365.

killed by violence and the like, a few contracted fibrous glomeruli, and other evidences of slight chronic interstitial nephritis were frequently found.

Naturally, the skin was first examined for lesions analogous to those occurring in the kidneys. They may be grouped under several headings:

1. *An increased number of cells*—lymphocytes, polynuclear leukocytes, or other cells—was seen only a few times, but there was no reason to connect them with the nephritis. No relation of such cells to the sweat glands could be demonstrated, with a single somewhat doubtful exception.

2. *An increase of fibrous tissue,* or thickening of the basement membrane about the sweat glands, was found only once in the 75 cases. In a structure so rich in fibrous tissue as the skin, this particular lesion is most difficult to determine.

3. *Desquamation* of the epithelial cells was also found exceedingly difficult to determine. In about 10 cases the epithelial cells of the secreting tubes were much shrunken and distorted. The alterations were certainly due in part to drying, which the exposed position of the skin makes possible; in part they were probably the result of active secretion shortly before death. The writer has seen a similar shrinking of the epithelium in normal skin from an amputated foot. In a few cases pathological desquamation had undoubtedly occurred. Some features suggested a relation between desquamation and shrinking of the epithelium from secretion. Postmortem changes seem to take place more easily in the epithelium of the secreting tubes than in that of the ducts. With the technique employed, the finer degenerative changes in cells would not be demonstrated. Actual necrosis of the epithelial cells, with loss of nuclear stain, was not seen at all.

4. *Cystic dilatation* of the secreting tubes was seen five times. In each case only one small cyst was discovered in several sections. In one of these it was associated with probable desquamation in other tubes and atrophy. Moderate dilatation of the ducts occurred four times; it seemed to be without pathological significance.

5. *Atrophy* of the secreting tubes, if present at all, was exceedingly rare. What appeared to be atrophy might have been collapse of the tubes after active secretion.

6. *Casts.* A small amount of amorphous, slightly stringy or granular material is quite often seen in the normal secreting tubes and ducts. In 17 cases (of the 75) homogeneous material, often taking the eosin stain, was seen in the ducts or, more rarely, in the secreting tubes. In cross-section such bodies could hardly be distinguished from casts in renal tubules. In longitudinal section they were never found to be unbroken along a considerable length, as is the case with renal casts. Usually, only one such body could be found in many sections. These bodies occurred several times in association with kidney lesions of the most trifling character. As the sweat glands are stated to secrete an oily substance, it is very doubtful that the bodies in question have at all the same significance as casts in the tubules of the kidney. Very rarely they contained cells or were composed of desquamated epithelium.

7. *Thrombosis.* Recent thrombi of the large arteries or veins were noticed frequently; old calcified thrombi of small veins four times. The recent thrombi were regarded as agonal, and none of the thrombi were in the vicinity of the sweat glands or seemed to have any relation to them. Small amorphous masses, hyaline or calcified, or both, were seen twice in the connective tissue of the true skin, apparently in lymph spaces. Their significance could not be determined, but they seemed to have no relation with the sweat glands.

8. *Arteriosclerosis* or *hyaline degeneration* of the arteries of the skin occurred in some degree sixteen times (in the 75 cases). The changes in the arteries were sometimes, though not usually, seen in the vessels supplying the sweat glands; but on prolonged search they would probably be found near the sweat glands in all cases that showed arteriosclerosis in the skin. No frequent association of the arterial changes with edema could be demonstrated. As the observations were made chiefly on skin from the sole of the foot, it is possible that they do not represent correctly the frequency of arteriosclerosis over the skin of the body in general. In part of the cases, skin from the middle of the abdominal wall was also studied, and changes in the arteries were found there much less often than in the foot. However, since the middle of the abdomen is poorly supplied with arteries, it cannot be regarded as a satisfactory control to the plantar region.

Thickening, with increase in the number of the connective tissue cells, in the walls of the small veins was seen ten times in the 75 cases; in four instances it was associated with old thrombosis of these veins. While it sometimes occurred in cases that showed arteriosclerosis, it was also observed independently. It is likely that the changes in the veins were partly due to local conditions in the foot. Similar changes have been observed by the writer in skin from the foot in normal subjects.[1]

9. Finally, there remains to be described a condition of the sweat glands of whose meaning I am uncertain. Text-books on histology seem to agree that the secreting portions of the coiled tubules of normal sweat glands are lined by a single layer of cubical or columnar epithelial cells. In the cases included in this study the secreting tubes sometimes were lined apparently by more than a single layer of cells. The cells were so irregularly disposed that it could hardly be said that they were arranged in layers, but, roughly speaking, they appeared to be two or three layers deep. The outlines of the individual cells were often difficult or impossible to distinguish. The condition occurred at scattered points and only for a short distance along a tubule, as was shown by the examination of serial sections. The whole diameter of the tubule was large, but not larger than is often seen in normal cases; the lumen was small, often very small. That such tubules were secreting tubules, and not ducts, was proved by their large size, the distinct basement membrane, and the muscle cells within the basement membrane. It was, naturally, exceedingly difficult to prove that the appearance of having several layers of cells might not have been produced by having cut across the coiled tubules obliquely. At the suggestion of Dr. Huber, I tried reconstructing a portion of some of the tubes under discussion, but found that the direction changed so continually, not in one, but in several planes, that it could hardly be said that any section was a true transverse section of a tubule. Furthermore, the course of the lumen often was more tortuous than that of the tubule as a whole. I have found secreting tubules lined by epithelial cells, apparently in several layers in skin from normal cases, but rarely and in a less

[1] See Martin, Peripheral Phlebosclerosis, Trans. Assoc. Amer. Phys., 1905, xx, 525.

marked degree. The impression obtained from comparison of normal cases and cases of nephritis has been that the latter do actually show increase in the number of the epithelial cells in the tubules; and that the same may possibly occur to some extent in normal cases. As stated in the first part of this paper, its weakest point is acknowledged to be the lack of an adequate number of normal cases for comparison. In a measure, this lack is compensated for by skin from mild cases of nephritis. In 14 cases of nephritis counted as mild or trifling, the epithelial cells of the secreting tubes of the sweat glands appeared to be in more than one layer only once; the same occurred fifteen times in 61 cases of nephritis regarded as moderate or severe.

Assuming that the epithelial cells actually are in layers, the significance of the change could only be conjectured. There is no evidence pointing to degeneration or desquamation; although no mitoses were seen, there appeared to be an increase in the number of cells. That, of course, does not prove the existence of a functional hypertrophy of the sweat glands. It is interesting, however, to recall that Köster and others allege that the glomeruli and tubules of the kidney may become hypertrophied in chronic nephritis. It is also possible that contraction of the longitudinally disposed muscle fibers beneath the epithelium might shorten the tubule and throw the epithelium into layers. I must also state again that the observations have been made almost exclusively on skin from the sole of the foot. The histories of hospital cases could not be relied upon to record such a symptom as hyperidrosis if it had been present.

Summary. The condition just described (¶ 9) will evidently require a long series of investigations for its explanation, so that a tentative presentation may be admissible now. The remainder of the work may be summarized by saying that in 75 cases of nephritis where skin from the sole of the foot was studied, arteriosclerosis was the only lesion that occurred in connection with the sweat glands frequently enough to be of great importance. Although bodies resembling casts in the renal tubules were not rare in the sweat glands, it is very doubtful that they have the same significance as renal casts or that they are pathological. Desquamation of epithelium, an increase of cells about the tubules suggesting inflammation,

and thickening of the fibrous tissue about the tubules were uncommon changes. While two or more of the conditions above described were sometimes seen associated in a single case, no important connection between them could be demonstrated. It seemed best to limit the scope of the present paper to an enumeration of the findings, leaving any conclusions that may be drawn for a subsequent report after more extended studies.

I am indebted to Dr. Charles G. Stockton for the suggestion that led me to undertake this work.

DISCUSSION.

Dr. A. S. Warthin: I should like to ask Dr. Williams if his attention has as yet been called to the great frequency of these pathological changes in the sweat glands. I believe they are very common. I have examined many sweat glands from the axillæ, and pathological changes are very common in them, particularly of the type mentioned. Cysts of inflammatory origin, hyperplasia, and formation of casts which really have to be distinguished from the horny layer of the ducts are very common findings. It is difficult to draw any relationship between any pathological changes occurring in the kidneys and the very frequent changes that occur in the sweat glands in such a great variety of diseases.

Dr. Williams: I am acquainted with the condition referred to in the coiled sweat glands, but have not come to any conclusions so far. Skin from the sole of the foot was selected because it was a region that was free of hairs and in all ways served the purpose better. For comparison, I have worked with the skin of normal individuals also. I have attempted to secure persons with perfectly normal kidneys, which are very rare in autopsy work. But, so far as it was possible, I have done so. I agree with Dr. Warthin that studies made on skin taken from the axillary region are practically worthless.

ON THE RELATION OF COMBINED INTOXICATION AND BACTERIAL INFECTION TO NECROSIS OF THE LIVER, ACUTE YELLOW ATROPHY, AND CIRRHOSIS.[1]

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Experiments have shown that various toxic substances administered to animals produce degenerative changes in the liver and, when this administration is prolonged during a considerable period, increase of the interstitial tissue follows. Nevertheless, the results of such experiments have been inconstant and the lesion which has been obtained has rarely possessed the clinical and anatomical characters of the cirrhosis common in man. In the attempt to produce cirrhosis alcohol has been repeatedly employed because it is believed to be the common cause of hepatic disease; phosphorus has been employed because it quickly produces advanced degenerative changes both in man and in animals.

Nevertheless a clear knowledge of the conditions upon which the occurrence of cirrhosis depends has not been obtained. Alcohol has been regarded as the most frequent cause of the disease, yet, on the one hand, it is well known that a history of excessive use of alcohol is obtained in little more than 50 per cent. of instances of cirrhosis; that the disease occurs in children some of whom have had no opportunity to use alcohol in any form. On the other hand, cirrhosis occurs in only a small proportion of those who are addicted to the use of alcoholic drinks; it was present in only 5 or 6 per cent. of the alcoholics examined by Baumgarten.[2] Degenera-

[1] Presented before the Philadelphia Pathological Society, March 10, 1910.
[2] Verhandl. d. deutschen path. Gesellsch., 1908, xi, 229.

tive changes in the liver indicated by infiltration with fat is more common.

Among the large number of those who have tested the effect of long-continued administration of alcohol upon animals a few have claimed that they have been able to produce increase of the interstitial tissues of the liver. Straus and Blocq[1] found the portal spaces infiltrated with cells and in some instances noted an increase of connective tissue at the periphery of the hepatic lobule. Mertens[2] allowed rabbits to breathe an atmosphere saturated with alcoholic vapor during periods as long as eleven months and twenty-eight days. In one group of animals which died after a few months there were degenerative changes in the parenchymatous cells, and although there was no increase of connective tissues, ascites was present; in a second group of animals which survived a longer period of administration, new interstitial tissue was found about the portal spaces and in certain instances extended from portal spaces to sublobular veins. These experiments were made upon rabbits; the spontaneous occurrence of cellular infiltration and of periportal cirrhosis referable to coccidia or other parasites is not infrequent, but does not explain all of the changes which have been found, Afanassijew[3] gave mixtures of ethyl and amyl alcohol to dogs, rabbits, and guinea-pigs, but failed to cause cirrhosis; v. Kahlden[4] used various animals, administering alcohol during periods up to 243 days, with like result. Friedenwald[5] found increase of interstitial tissue in some animals (rabbits), but in others which had received from 5 to 8 c.c. of alcohol during four years he observed no trace of cirrhosis. Other negative experiments might be cited; simple administration of ethyl alcohol fails to increase the interstitial tissue of the liver. Moreover, the production of changes indicating alteration of the hepatic cells has been inconstant and often trivial.

With the purpose of establishing a definite relation between intense degeneration of hepatic cells on the one hand, and new formation of fibrous tissue on the other, many attempts have been made

[1] Arch. de physiol., 1887, Series 3, x, 409.
[2] Arch. internat. de pharmacol., 1896, ii, 127.
[3] Ziegler's Beit., 1890, viii, 443.
[4] Ibid., 1891, ix, 349.
[5] Jour. Amer. Med. Assoc., 1905, xiv, 780.

to produce cirrhosis by continued administration of phosphorus. Acute poisoning with phosphorus, it is well known, is associated with intense fatty degeneration of the liver cells associated with some necrosis. Several observers, Aufrecht,[1] Krönig,[2] Ackermann,[3] and Dinkler,[4] have produced increase of interstitial tissue by repeated administration of small quantities of this poison. Ziegler and Oblonski failed to produce changes resembling cirrhosis of man, but Aufrecht[5] by prolonged administration has produced a nodular liver, which, he claims, exhibits the usual characters of human cirrhosis. New formation of fibrous tissue has its origin at the periphery of the lobule in contact with the portal spaces.

By means of hemagglutinative serum prepared by immunization of rabbits with the red blood corpuscles of the dog, Pearce[6] has produced in the dog agglutination of corpuscles within the hepatic capillaries and consequent irregularly distributed necrosis of hepatic parenchyma. The necrotic tissue is rapidly absorbed and replaced by connective tissue. Liver cells outside of the dead area undergo multiplication and newly formed structures resembling bile ducts penetrate the new interstitial tissue.

The prevailing view that proliferation of connective tissue is the consequence of injury and destruction of the parenchymatous cells of an organ has caused a few experimenters to administer chloroform with the purpose of reproducing human cirrhosis. The toxic effects of chloroform upon the liver is well known. The early observers have been doubtful whether the resulting lesion is intense fatty degeneration or necrosis, but subsequent study has shown that both may be caused by chloroform. The recent experiments of Howland and Richards[7] and of Whipple and Sperry[8] in this country have shown that anesthesia by chloroform continued from one to three hours and repeated on two or three successive days is followed by necrosis of the columns of liver cells occupying perhaps the central two-fifths of each lobule; the liver cells in im-

[1] Deutsches Arch. f. klin. Med., 1879, xxiii, 331.
[2] Virchow's Arch., 1887, cx, 502.
[3] Ibid., 1880, lxxv, 396.
[4] Inaug. Diss., Halle, 1887.
[5] Deutsches Arch. f. klin. Med., 1897, lviii, 302.
[6] Jour. Exper. Med., 196, viii, 64; Jour. Med. Research, 1906, xv, 99.
[7] Jour. Exper. Med., 1909, xi, 344.
[8] Johns Hopkins Hosp. Bull., 1909, xx, 278.

mediate contact with the portal spaces alone remain intact and occasionally the entire hepatic substance save a narrow fringe of cells about each portal space is destroyed. Fatty degeneration accompanies necrosis and occurs where the action of the poison is not sufficiently intense to produce cell death. With mild poisoning the centre of each lobule exhibits fatty degeneration instead of necrosis, and in some instances central fatty degeneration and necrosis occur in the same liver.

The extensive necrosis of the liver caused by chloroform offers an opportunity to test the relation of cirrhosis to degenerative changes in the hepatic parenchyma; to determine to what extent necrotic parenchymatous cells are replaced by fibrous tissue. The experiments of Whipple and Sperry are particularly instructive. Anesthesia with chloroform, for example, during three hours on one day or during two and a half hours on three successive days, has been followed by hyaline necrosis of the central three-fifths of each hepatic lobule; the extent of necrosis has been determined by removal of a bit of liver tissue on the day following the last anesthesia. The animal recovers completely, and examinations made at the end of one, two, and three weeks have shown that repair is almost complete after two weeks, whereas at the end of three weeks the liver has returned to normal. Mononuclear phagocytic cells invade the area of coagulative necrosis and ingest particles of dead hepatic cells. Mitotic nuclear figures within the surviving hepatic cells show that regeneration is in progress and columns of liver cells elongate to replace those which have been destroyed. There is no new formation of fibrous tissue and no cirrhosis follows destruction of more than half of the entire organ.

Nevertheless, the literature of the subject contains records of experiments in which cirrhosis of the liver has been produced by chloroform. Mertens (1896) has produced cirrhosis in rabbits by daily subcutaneous injection of small quantities of chloroform (0.1 to 0.2 c.c.) dissolved in liquid paraffin, continued in some instances as long as six months. The liver becomes pale and hard and in some instances has the nodular appearance of atrophic cirrhosis. The parenchymatous cells undergo various forms of degeneration and bands of newly formed fibrous tissue traverse the organ. Ac-

cording to Mertens, the new bands of fibrous tissue have their origin about the portal spaces at the periphery of the lobules, but later unite neighboring portal spaces and are continuous with the tissue about the hepatic veins. Herter and Williams[1] have produced cirrhosis in dogs by similar means. After inhalation of chloroform during a period from an hour to an hour and a half, on twenty-four occasions within eight weeks, the liver contained abundant cellular connective tissue between and within the lobules; bile ducts had undergone proliferation and fatty hyaline liver cells were abundant. Two other experiments had a similar result.

The experiments of Whipple and Sperry, who found complete restoration to normal after extensive necrosis, have suggested that recovery occurs because regeneration of parenchyma is active and uninterrupted. Numerous experiments have shown that chloroform administered by stomach has the same effect as when administered by inhalation. A dose of from 0.5 to 1 c.c. per kilogram of body weight repeated on three successive days usually produces well-marked necrosis of the central part of the lobule. After an interval of three days, necrotic cells are in large part removed, the central part of the lobule is infiltrated with numerous cells, in part mononuclear phagocytes, and healing is in progress. This process may be interrupted by a further administration of chloroform repeated, as before, on successive days. Such continued insults to the organ, repeatedly producing grave degenerative change, are followed by sclerosis, by regenerative change indicated by proliferation of parenchymatous cells and by abundant new formation of structures resembling bile ducts.

The following experiments illustrate the sclerosis which may occur within the short period of two months.

A dog (Chlor. i) weighing 6250 grams has been given 1 c.c. per kilo on three successive days, followed by a rest of three days, in turn followed by chloroform, so that it has received in all 218 c.c. of chloroform. It has become slightly jaundiced and the superficial abdominal veins have been considerably dilated. At autopsy the veins of the portal system are dilated, the tissue about the pancreas is

[1] Proc. of the Soc. for Exper. Biol. and Med., 1905, iii, 23.

œdematous, and the peritoneal cavity contains a small quantity (6 c.c.) of fluid. The liver is small (weighing 185.5 grams = $\frac{1}{35}$ of original body weight), yellow, and resistant to the knife.

Examination has shown that about one-third of the sectional area consists of very cellular, newly formed connective tissue (Fig. 1) situated about the central veins and in contact with the sublobular vessels. The liver cells are in columns which radiate from the

FIG. 1.—Showing cirrhosis of the liver, with new formation of bile ducts, caused by administration of chloroform during two months (Dog. Chlor. i).

portal spaces; they have the appearance of regenerating hepatic parenchyma, the columns being formed by regularly disposed cells in double row with the nuclei regularly arranged along either margin of the column. Mitotic figures occur, but they are not

numerous. Near the centre of lobules within the new fibrillated tissues are so-called newly formed bile ducts composed of cubical cells forming well-defined tubules.

Increase of fibrous tissue has been associated with portal obstruction and serous transudation. The newly formed fibrous tissue occupies that part of the lobule which is the site of necrosis caused by chloroform. Active regeneration of parenchyma and new formation of bile ducts having no relation to those in the portal spaces has occurred.

A second experiment is noteworthy because the same poison administered by a somewhat different method has produced a wholly different lesion.

A large animal (Chlor. iv) weighing 10,100 grams has received 2 c.c. of chloroform per kilo on three successive days; a rest of six days has been followed by chloroform repeated as before; the animal has died at the end of sixty days after it has received 424 c.c. of chloroform. The liver is fairly large (weighing 394 grams = $\frac{1}{26}$ of original body weight), with superficial indentation corresponding to the lobulation, and has a bright canary-yellow color.

Thick bands of cellular fibrous tissue traverse the organ; they are usually in the centre of the lobule, but their position is often obscure. The parenchyma is the site of intense fatty degeneration, almost every cell being swollen and distended with fat. Newly formed bile ducts are rarely found. The lesion reproduces with fair accuracy the cirrhosis with fatty degeneration which is believed to occur as the result of excessive drinking of beer.

In another experiment which may be cited, the animal has lived longer.

A dog (Chlor. iii) weighing 9150 grams has lived three months and has received approximately thirty-two doses of 1 c.c. per kilo (= 393.5 c.c. chloroform). There has been jaundice and dilation of superficial abdominal veins. Veins of the portal system are dilated and the peritoneal cavity contains serous bile-stained fluid (14.5 c.c.). The liver (weighing 422 grams = $\frac{1}{22}$ of original body weight) is pale yellow.

Whereas fibrous tissue in proportion to sectional area is not so abundant as in preceding experiments, it is denser and poorer in

cells. The relation of newly formed tissue to central veins is apparent, but less conspicuous than in the other experiments, for the normal lobulation is much distorted. In some places patches and bands of fibrous tissue may be in contact with portal spaces. Small islands of parenchyma may be completely surrounded by fibrous tissue, and in many places fine bands of new tissue penetrate between columns of liver cells.

The lesion which has been described begins in the centre of the lobule and surrounds the central vein; the relationship between new formation of fibrous tissue and necrosis of parenchyma is obvious. Nevertheless, long continued recurring injury, with destruction and regeneration of parenchyma, tends to distort the normal architecture of the gland so that lobulation becomes obscured. Advanced cirrhosis has occurred with considerable rapidity, and degeneration of parenchyma has been much more conspicuous than regeneration. The regenerative changes which, associated with contraction of the newly formed fibrous tissue, give to the liver of atrophic cirrhosis its nodular appearance have not been produced, and the liver in all of these experiments has been fairly smooth, with, at most, fine granulation, corresponding to the disposition of the lobules.

It has long been known that the liver bears a peculiar relation to bacterial infection. The endothelial cells lining the capillaries of the liver and the neighboring stellate cells are capable of active phagocytosis, and, as Wyssokowitch[1] found more than twenty-five years ago, take up bacteria injected into the circulating blood. Experiments of Welch and Blachstein[2] showed that Bacillus coli and typhoid bacillus injected into the veins of a rabbit appear in the bile and may persist for weeks in the gall-bladder. Numerous experiments have subsequently confirmed these observations. Experiments of Buxton and Torrey[3] show that typhoid bacilli injected into the peritoneal cavity quickly enter the blood and are deposited in various organs. At the end of an hour the number in the blood is small; plating on agar shows that the number which accumulates in the liver is far greater than that in other organs.

[1] Zeit. f. Hyg., 1886, i, 1.
[2] Johns Hopkins Hospital Bull., 1891, ii, 96.
[3] Jour. of Med. Research, 1906, xv, 18.

Central necrosis implicating from half to three-fifths, or even more of each lobule, and identical with that produced by chloroform, is not infrequently found in the liver of individuals dying with a considerable variety of conditions. Mallory found the lesion ninety-five times among 1190 autopsies, usually in association with acute bacterial infection, such as acute endocarditis, lobar pneumonia, peritonitis, diphtheria, etc. In approximately one-half of the cases in which there was bacteriological examination, Streptococcus pyogenes was isolated; other microörganisms, such as Diplococcus lanceolatus, Bacillus diphtheriæ, and Staphylococcus aureus, have been found. Mallory has expressed the opinion that the lesion is due to the presence of a circulating toxin, most frequently derived from the streptococcus.

Several years ago I noted a remarkable lesion occurring in the liver of a child who had died with general peritonitis following gonorrheal infection.[1] A conspicuous circle of hyaline necrosis occurred in each lobule in a zone separated by living cells both from the central vein and from the portal spaces. Examining the livers from nearly 1000 autopsies, I found 14 examples of this lesion, which may be termed mid-zonal necrosis. The lesion is accompanied by fatty degeneration of the hepatic cells in the centre of the lobule and occasionally of the cells at the periphery of the lobule in contact with the portal spaces as well. The lesion has been associated with acute suppurative conditions (general peritonitis in 6 instances, operative or ulcerative lesions of the gastro-intestinal tract in 3, general pyemic infection in 3, etc.), and in 11 instances bacteriological examination has shown the presence of staphylococcus (in 6), Bacillus coli (in 3 alone, in 2 combined with streptococcus), or Bacillus proteus vulgaris (in 2). The infrequency of the lesion and the frequency of severe bacterial infection indicate that the association of some undetermined factor, perhaps some disturbance of metabolism, is essential for its production.

The experimental reproduction of this peculiar lesion will serve to show that the effect of bacterial infection may be profoundly modified by the presence of a toxic substance which has entered the blood.

[1] Jour. of Med. Research, 1904, xii, 147.

A large dog (Chlor. xviii) weighing 15,200 grams has been given 7.6 c.c. of chloroform (0.5 c.c. per kilo) on four successive days; on the fifth day, 0.5 c.c. of a twenty-four-hour bouillon culture of Bacillus coli has been injected into the jugular vein. On the eighth day, chloroform has been again administered. The animal has been killed on the following day. The liver is large, and deep red; after blood has partially escaped from the tissue, the centres of the lobules are yellow. Lymphatics upon the surface of the gall-bladder are conspicuously dilated; the bile contains Bacillus coli in pure culture.

The central part of each lobule, occupying one-half the space from central vein to portal space, exhibits fatty degeneration, the cells being filled with fine vacuoles. At the periphery of the lobule liver cells are well preserved, and contain only a few fat droplets. In a conspicuous but narrow intermediate zone, forming a circle within each lobule, liver cells have undergone hyaline necrosis, have lost their nuclei, and stain bright pink with eosin.

It is noteworthy that the same peculiar mid-zonal necrosis may be reproduced experimentally by another poison, namely, phosphorus in combination with another bacterium, Streptococcus pyogenes, in another animal, the rabbit. The following experiment illustrates very clearly the susceptibility of injured liver to bacterial infection:

Four animals (Rabbits Phos. 2, 3, 5, and 6) received $\frac{1}{50}$ grain of phosphorus by mouth daily; during several days administration was suspended, so that each animal received during twenty-four days $\frac{14}{50}$ grains. Two of these animals were repeatedly inoculated in the ear vein with Streptococcus pyogenes; these animals died on the same day, twenty-four days after the beginning of the experiment, and the two animals which received phosphorus alone were killed.

Save for trivial fatty degeneration, the livers of the two animals (Rabbits Phos. 2 and 3) which received phosphorus alone exhibit no noteworthy change (Figs. 3 and 5). Those which have received streptococcus exhibit advanced degenerative changes, causing injury or destruction of the entire hepatic parenchyma. In one (Rabbit Phos. 6), in which the changes are more profound, there is diffuse fatty degeneration accompanied by hyaline necrosis, and hemorrhage in the centre of the lobules (Fig. 4). In the second infected

animal (Rabbit Phos. 5), the centre of each lobule exhibits fatty degeneration; about this central fatty tissue is a conspicuous ring of hyaline necrotic cells which separates the fatty cells in the centre from a relatively normal peripheral zone in contact with the portal spaces (Fig. 2). This lesion, which is produced neither by the

FIG. 2.—Showing mid-zonal necrosis of the liver in a rabbit (Rabbit Phos. 5) which has received both phosphorus and streptococci.

poison nor by the bacterium acting alone, demonstrates the peculiar effect of bacterial infection upon an injured liver.

The effect of hepatic injury upon the progress of bacterial infection has been little studied. Adami[1] in America, and Hanot[2] and others in France, have maintained that cirrhosis of the liver may be referable to chronic bacterial infection. The experimental pro-

[1] Brit. Med. Jour., 1898, ii, 1215; Jour. of the Amer. Med. Assoc., 1899.

[2] Compt. rend. Soc. de biol., 1893, xlv, 741; XI Internat. med. Cong. zu Roma; Berliner klin. Woch., 1894, xxxi, 479.

duction of cirrhosis by administration of toxic substances such as chloroform and phosphorus proves that introduction of bacteria is not essential. Repeated inoculations with various bacteria usually fail to increase the interstitial tissue of the liver; some observers have found increase of the interstitial tissue of the liver after injec-

FIG. 3.—Showing the relatively normal liver of an animal (Rabbit Phos. 2) which has received phosphorus alone (in quantity corresponding with that administered to Rabbits Phos. 5 and 6). For comparison with Figs. 2 and 4.

tion of various microörganisms (Scagliosi,[1] Dantschatoff-Grigorevski,[2] Bjorksten[3]), but the change has usually been associated with suppurative cholangitis, and increase of interstitial tissue has occurred about the portal spaces. Bacteria capable of causing cirrhosis in animals have been isolated by Weaver[4] and by Hektoen.[5]

[1] Virchow's Arch., 1896, cxlv, 546. [2] Cent. für. allg. Path., 1904, xv, 667.
[3] Arbeiten a. d. path. Inst. z. Helsingfors, 1902, 209.
[4] Contributions to the Science of Medicine Dedicated to Wm. H. Welch, Reports of the Johns Hopkins Hosp., 1900, xi, 297.
[5] Jour. of Path. and Bact., 1901, vii, 214.

In a series of experiments I have attempted to modify the effect of chloroform by accompanying injection of certain bacteria. By this means I have succeeded in producing lesions of a character and intensity not obtained by simple administration of chloroform. This statement is illustrated by the following experiment.

FIG. 4.—Showing fatty degeneration and necrosis of the liver in a rabbit (Rabbit Phos. 6) which has received both phosphorus and streptococci.

A dog (Chlor. xvii) weighing 16,650 grams has received on four successive days 8.3 c.c. of chloroform (0.5 c.c. per kilo); on the fifth day, 0.5 c.c. of a twenty-four-hour bouillon culture of Bacillus coli has been injected into the jugular vein. The animal has received subsequently six doses of chloroform (0.5 c.c. per kilo), and has died on the twenty-third day of the experiment, twenty-four hours after a second injection of Bacillus coli (0.25 c.c.). There has been well marked jaundice. The liver is smooth; pale yellow tissue surrounds hemorrhagic spots occupying the centres of the lobules.

Bacillus coli has not been recovered from the liver, bile, heart's blood, or kidney.

Almost the entire hepatic parenchyma has undergone disintegration and is represented by a narrow zone of intact cells encircling each portal space (Fig. 6). These cells exhibit moderate infiltra-

FIG. 5.—Showing the relatively normal liver of an animal (Rabbit Phos. 3) which has received phosphorus alone (in quantity corresponding with that administered to Rabbits Phos. 5 and 6). For comparison with Figs. 2 and 4.

tion with fat. In a few places the supporting framework of the lobule remains and endothelial cells persist, but elsewhere all hepatic architecture is lost and an almost structureless groundwork is infiltrated with lymphoid cells, large mononuclear cells, polynuclear leukocytes, red blood corpuscles in great number, and remains of liver cells. In an intermediate zone between this central tissue and the thin fringe of intact liver cells about the portal spaces, there is conspicuous hyaline necrosis of liver cells (Fig. 7) which, frag-

mented and scattered, have lost their nuclei and stain brightly with eosin. Proliferation of connective tissue is in progress and cells having the characters of fibroblasts are abundant in contact with the living tissue about the portal spaces. The presence of numerous newly formed tubules resembling bile ducts affords evidence of

FIG. 6.—Photograph of the liver of a dog (Chlor. xvii), showing a lesion resembling acute yellow atrophy of the liver; there is necrosis of parenchyma and beginning new formation of bile ducts.

proliferation of parenchymatous elements (Figs. 6 and 7). These tubules, at times obviously continuous with surviving columns of cells, are pushing their way from the periphery to the centre of the lobule. Occasionally, groups of such tubules occur near what has been the centre of the lobule; in such places there is delicate connective tissue rich in cellular elements.

The lesion in this experiment has reproduced, with considerable accuracy, certain instances of acute yellow atrophy with beginning regeneration of parenchyma. Part of the tissue is necrotic and

hemorrhagic, whereas a small part is intact and the site of fatty change. Fibrous tissue has begun to encroach upon the zone of necrosis and active proliferation of bile ducts is in progress.

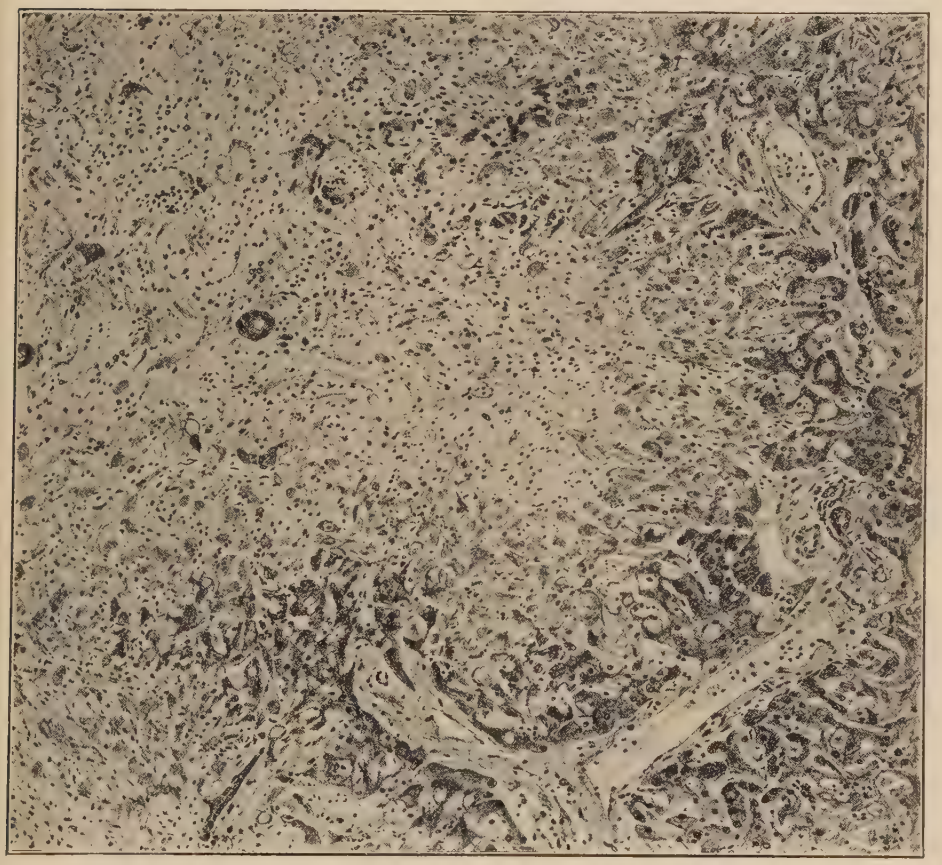

FIG. 7.—Drawing of the liver from the same animal (Chlor. xvii), with higher magnification, showing isolated bile ducts in the loose connective tissue, which has partially replaced the necrotic parenchyma in the central part of the lobule. There is a narrow zone of intact parenchyma in contact with the portal spaces. In an intermediate zone there is hyaline necrosis.

In order to test the effect of bacterial infection upon production of cirrhosis by chloroform, two animals have been given equal quantities of chloroform, and one has received bacteria injected into the jugular vein.

A dog (Chlor. xxii) weighing 10,550 grams has received 10 c.c. of chloroform (1 c.c. per kilo) on three successive days; on the fourth day of the experiment it has lost 850 grams of body weight. On the eighth, ninth, thirteenth, and fifteenth days it has received 10 c.c. of chloroform; on the twenty-first and twenty-second, 5 c.c. The

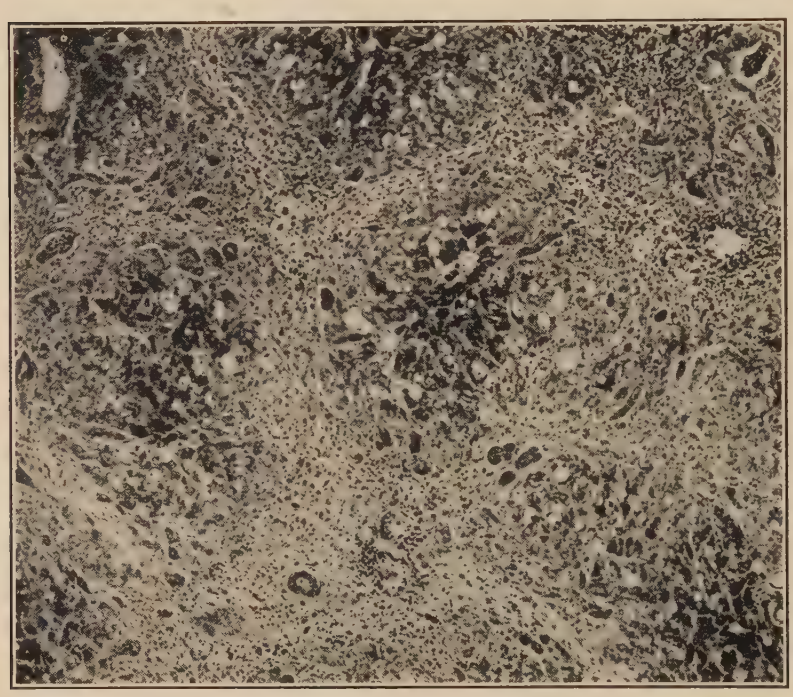

FIG. 8.—Photograph of the liver of a dog (Chlor. xxiii) which has received chloroform plus Bacillus coli injected intravenously. There is advanced cirrhosis with new formation of bile ducts twenty-three days after the beginning of the experiment.

animal has been killed on the twenty-fourth day. The liver is large (weighing 513 grams = $\frac{1}{21}$ of the original body weight) and pale yellow in color. There is no evidence of portal obstruction. Agar-agar inoculated from the liver, bile, and kidneys remains sterile.

A dog (Chlor. xxiii) weighing 10,500 grams has received chloroform in quantities and at intervals identical with those recorded for the preceding animal. On the fourth day of the experiment it has lost 500 grams of body weight and has received into the jugular vein 0.5 c.c. of a twenty-four-hour bouillon culture of Bacillus coli. On

the day following inoculation the animal has been very sick and for a time has appeared to be moribund. After the eleventh day of the experiment there has been jaundice. Death has occurred on the twenty-fourth day. The veins of mesentery and omentum are moderately distended, the pancreas is œdematous throughout, and the peritoneal cavity contains 21 c.c. of serous fluid. Bacillus coli has been cultivated from the kidney, but not from the liver or bile. The liver is small (309 grams = $\frac{1}{34}$ of original body weight) and pale yellow, with lobulation sharply marked by yellow zones surrounding red spots.

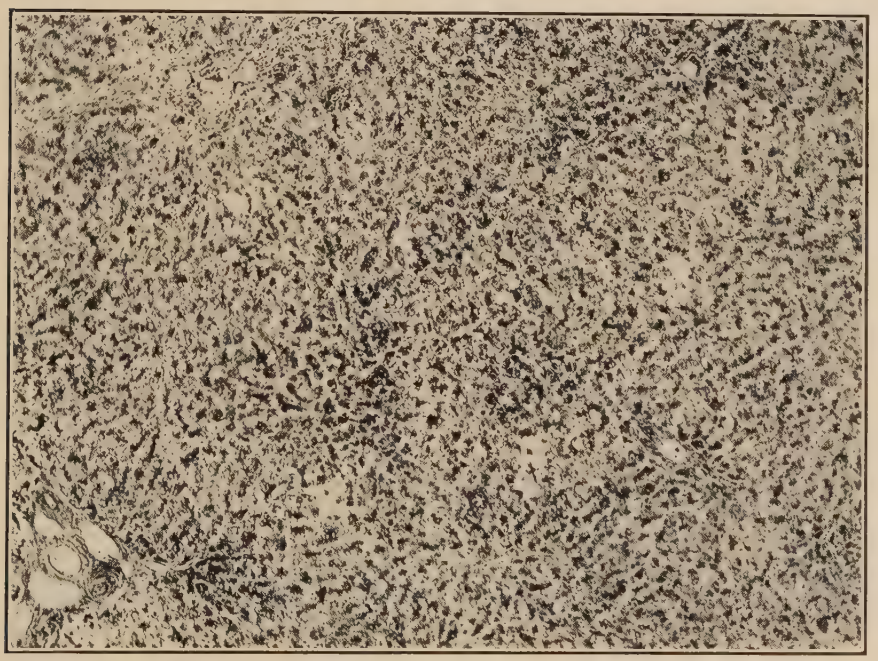

Fig. 9.—Photograph of the liver of a dog (Chlor. xxii) which has received chloroform alone, administered in a quantity equal to that received by Dog Chlor. xxiii. There is diffuse fatty degeneration. For comparison with Fig. 8.

In the liver of the animal (Dog Chlor. xxii) which has received chloroform alone, there is advanced, diffusely distributed fatty degeneration of the hepatic parenchyma (Fig. 9). Fibrous tissue in immediate contact with some of the central veins is slightly thickened,

and here are collected a few polynuclear leukocytes and small round cells, but changes affecting the interstitial tissue are trivial.

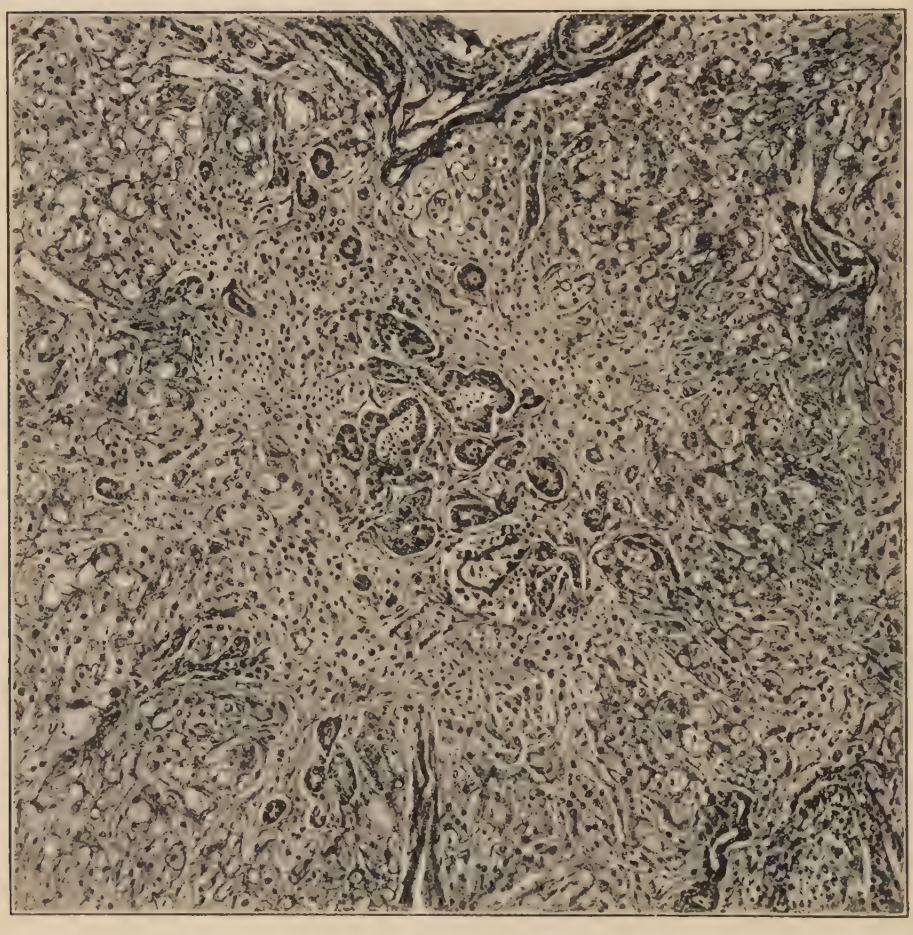

Fig. 10.—Drawing of the liver (Chlor. xxiii) shown in Fig. 8. Newly formed fibrous tissue most abundant about the central vein of the lobule (see centre of figure) replaces and divides the parenchyma. There is enormous proliferation of bile ducts and polynuclear leukocytes are abundant within the larger of the new ducts which occupy the central part of the lobules.

In the liver of the animal (Dog Chlor. xxiii) which has received both chloroform and Bacillus coli, on the contrary, masses and strands of cellular fibrous tissue subdivide the parenchyma into islands of which the relation to the original lobules is not always

evident (Fig. 8). This new connective tissue forms at least half of the sectional area. About portal spaces fibrous tissue is not increased and, though central veins are often unrecognizable, contact with a portal space often shows that the central part of the lobule is occupied by fibrous tissue containing a group of tortuous and enormously hypertrophied bile ducts obviously newly formed (Fig. 10). A circular zone of intact but fatty parenchyma often surrounds this central area. Small newly formed bile ducts radiate from this zone of parenchyma toward the central group of ducts. The smaller ducts are formed by low flat or cubical cells, but the larger more central ducts are formed by high columnar cells and have a wide lumen often filled with polynuclear leukocytes. The enormous multiplication of these duct-like structures is shown in the figures (Figs. 8 and 10).

A quantity of chloroform which alone has caused only fatty degeneration has, in association with a single large dose of Bacillus coli, produced advanced hepatic cirrhosis within a period of twenty-three days. A noteworthy feature of the lesion reproduced in subsequent experiments with Bacillus coli is the active proliferation and hypertrophy of bile ducts newly formed in situations far removed from the bile ducts of the portal spaces. Cirrhosis and multiplication of bile ducts is far more advanced at the end of twenty-three days than in those experiments in which larger doses of chloroform unaccompanied by bacterial infection have been continued during two or three months.

In the following experiments, administration of chloroform in relatively small amounts has been accompanied by bacterial inoculation.

A dog (Chlor. xxi) weighing 7550 grams has received 15.2 c.c. of chloroform (2 c.c. per kilogram of body weight), and on the following day 0.5 c.c. of a twenty-four-hour bouillon culture of Bacillus coli. It has subsequently received twelve doses of 7.1 c.c. of chloroform, the total amount of chloroform administered being 104.5 c.c. and two injections of Bacillus coli (0.04 and 0.3 c.c.). There has been jaundice. Death has occurred at the end of thirty days. The liver is pale yellowish brown and weighs 260 grams ($\frac{1}{29}$ of original body weight).

In sections for microscopic examination, the central part implicating approximately one-third of each lobule is replaced by loose cellular connective tissue containing many mononuclear cells. Where well-preserved columns of liver cells are in contact with this cellular tissue there are tubules composed of cubical cells, arranged about a conspicuous lumen; these tubules, though larger, have the characters of the bile ducts in the portal spaces, but are separated from them by a wide zone of hepatic parenchyma. It is not improbable that this animal received its first injection of bacteria at a time when the liver was little injured, and subsequent small quantities of bacteria have had little effect upon the partially immunized animal.

In another experiment, a dog has received an immunizing dose of Bacillus coli and has subsequently received chloroform together with small quantities of Bacillus coli injected into the jugular vein.

A dog (Chlor. xxiv) weighing 5750 grams has received 0.5 c.c. of a twenty-four-hour bouillon culture of Bacillus coli. Sixteen days later, doses of chloroform (5 c.c.) have been given on three successive days; on the following day, the animal has received a very small quantity of Bacillus coli (0.01 c.c. of a bouillon culture). Later, chloroform has been administered interruptedly; in all, 72.25 c.c. of chloroform have been given in seventeen doses of 1 or 0.5 c.c. per kilogram of body weight during forty-three days. Following the second injection of bacteria, small quantities of Bacillus coli (0.02, 0.02, 0.1, 0.05, 0.1, 0.1, and 0.2, 0.25 c.c., respectively, at intervals of from three to ten days) have been injected into the jugular vein. Death, preceded by jaundice, has occurred forty-three days after the first administration of chloroform. The liver is pale reddish yellow and relatively large (245 grams = $\frac{1}{24}$ of original body weight).

The parenchyma of the liver has undergone advanced degenerative change, so that only a few cells in immediate contact with the portal spaces exhibit the usual staining characters of liver cells; even here the cells are finely vacuolated, but elsewhere all living cells are distended with large vacuoles, indicating advanced diffusely distributed infiltration with fat. Scattered among these fatty cells and more abundant near the central vein are numerous conspicuous groups of liver cells and remains of cells which have undergone

hyaline necrosis. Such cells have lost their nuclei or contain particles of structureless nuclear substance. There is no newly formed connective tissue, but particularly in the central part of the lobule there is infiltration with small and large mononuclear cells and with polynuclear leukocytes. A noteworthy feature of the organ is the presence of numerous newly formed bile ducts, which are thickly scattered between the fatty liver cells and occur in the absence of new formation of interstitial tissue. In some instances these ducts are composed of cubical cells and have an inconspicuous lumen; in other instances, they are formed by high columnar cells ranged about a conspicuous lumen. Such newly formed bile ducts are more numerous near the centre than at the periphery of the lobule, and no relationship to bile ducts within the portal spaces can be found.

In order to determine if the strain of colon bacillus which has been employed in the foregoing experiments is capable of producing alone hepatic lesions, large quantities have been injected at frequent intervals into the jugular vein of two animals.

A dog (B. C. 5) weighing 7800 grams has repeatedly received intravenously injections of Bacillus coli grown twenty-four hours in bouillon as follows: First day, 0.2 c.c.; fifth, 0.1; eighth, 0.1; twelfth, 0.1; fifteenth, 0.25; twentieth, 0.5; twenty-fourth, 0.25; twenty-eighth, 0.25; thirty-first, 0.5; thirty-fifth, 0.5; forty-first, 0.5; forty-fifth, 0.5; forty-eighth, 0.5; fiftieth, 0.5; fifty-fourth, 0.5; sixty-first, 0.5. The animal has lost weight, weighing 5500 grams on the sixty-fifth day of the experiment; on this day it has been killed. The liver is large, weighing 420 grams ($\frac{1}{19}$ of original body weight), smooth, and pale reddish brown in color. The gall-bladder is small and its wall is thicker than usual; it contains clear yellow viscid bile in which are soft solid particles.

The hepatic cells are diffusely infiltrated with fat, but there are no other noteworthy changes in the liver.

A dog (B. C. 7) weighing 10,950 grams has received intravascular injections of bouillon cultures of Bacillus coli as follows: First day, 0.06 c.c.; fifteenth, 0.2; nineteenth, 0.1; twenty-sixth, 0.1; twenty-ninth, 0.25; thirty-fourth, 0.5; thirty-eighth, 0.5; forty-second, 0.5; forty-fifth, 0.5; forty-ninth, 0.5; fifty-fifth, 0.5; fifty-ninth, 0.5;

sixty-second, 0.5; sixty-fourth, 0.5; sixty-eighth, 0.5; seventy-fifth, 0.5. The animal has become thin and somewhat weak, weighing 8500 grams on the seventy-ninth day of the experiment; on this day it has been killed. The liver, weighing 394 grams ($\frac{1}{28}$ of original body weight), is smooth, soft, brownish red, and appears to be normal.

The liver shows infiltration with fat, but is otherwise normal.

Further evidence that the repair of hepatic necrosis may be retarded by bacterial infection has been obtained by the employment of streptococcus. The microörganism employed has been obtained from the heart's blood and liver of a man dying with vegetative endocarditis of the aortic valve, associated with atrophic cirrhosis of the liver. It forms long chains and in bouillon tends to grow in small clumps, which leave the medium clear.

In the following experiment two animals of approximately equal weight have received like quantities of chloroform administered in the same way to each animal. One of them has received repeated intravascular injection of Streptococcus pyogenes; a third animal has received Streptococcus pyogenes in the same quantity and at the same time.

A dog (Chlor. xxxii) weighing 8350 grams has received on three successive days 4 c.c. of chloroform (0.5 c.c. per kilogram of body weight); on the fourth day it had lost 450 grams of body weight. It has received the same quantity of chloroform on the seventh, eighth, twelfth, seventeenth, and eighteenth days of the experiment, the total quantity administered being 32 c.c. Following the last dose of chloroform there has been jaundice, which later has disappeared. The animal has been killed on the twenty-eighth day. There is a small amount of fluid (5 c.c.) in the peritoneal cavity and some œdema of the pancreas. The liver weighs 310 grams ($\frac{1}{27}$ of original body weight) and is reddish yellow in color. No bacteria grew from liver or bile.

A dog (Chlor. xxxi) weighing 8250 grams has received chloroform in quantity at intervals corresponding with those just described. Eight days before administration of chloroform, 0.08 c.c. of a twenty-four-hour bouillon culture of Bacillus coli has been injected into the jugular vein. Immediately after the first dose of chloroform, 0.025 c.c. of a similar culture has been injected intravenously. On the

fourth day after first administration of chloroform the animal has lost 200 grams of body weight, There have been subsequent injections of streptococci on the following days (dating from first administration of chloroform): seventh, 0.05 c.c.; thirteenth, 0.2 c.c.; nineteenth, 0.2 c.c.; twenty-first, 0.3 c.c.; twenty-fourth, 0.3 c.c. The animal has died on the twenty-eighth day. There is advanced

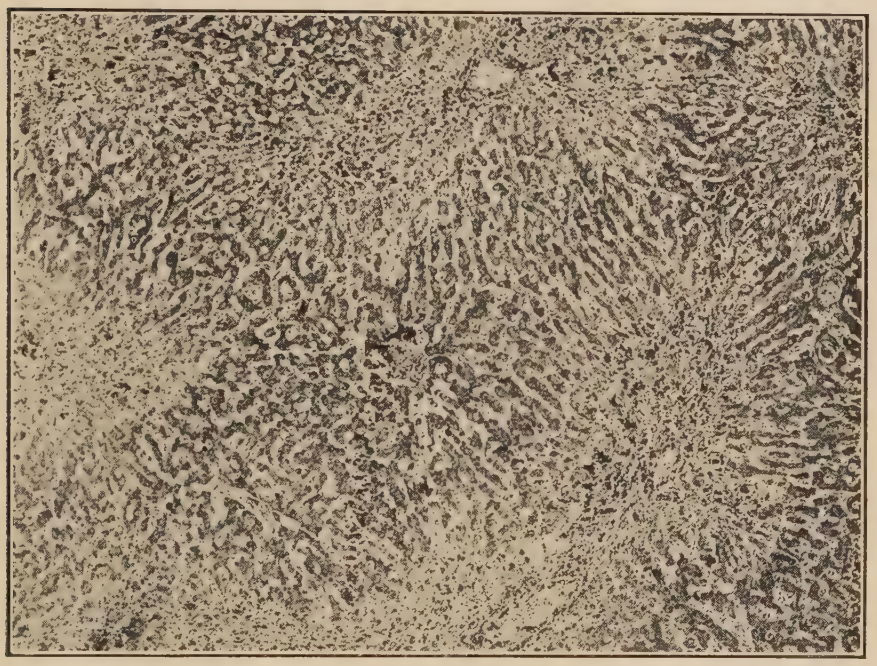

FIG. 11.—Photograph showing the liver of a dog (Chlor. xxxi) which has received chloroform and streptococci. The central part of each lobule is replaced by interstitial tissue.

suppurative pericarditis, the pericardial cavity being distended with 500 c.c. of seropurulent fluid. The liver weighs 238 grams ($\frac{1}{35}$ of original body weight) and is deep red. Culture media inoculated from the liver and bile remain sterile.

A dog (Chlor. St. xxxiii) weighing 10,550 grams has received streptococci in quantities corresponding with those administered on the first, seventh, thirteenth, nineteenth, twenty-first, and twenty-fourth days to the foregoing animal. On the twenty-eighth day the animal has been killed. The liver, weighing 410 grams ($\frac{1}{27}$ of the

original body weight), is normal in appearance. Culture media inoculated from liver and bile remain sterile.

In the animal which received chloroform alone (Chlor. xxxii) the liver cells exhibit advanced diffusely distributed fatty degeneration (Fig. 12). Within part of the lobules there is no other change, but in the centre of others about the central vein is loose-meshed

Fig. 12.—Photograph showing the liver of a dog (Chlor. xxxii) which has received chloroform in quantity equal to that received by Dog Chlor. xxxi. There is diffuse fatty degeneration and some increase of interstitial tissue. For comparison with Fig. 11.

connective tissue, containing widely dilated capillaries and a small number of large and small mononuclear cells. In the margin of this tissue in many places occur newly formed bile ducts.

In the animal which received both chloroform and streptococcus (Chlor. xxxi) changes in the liver are considerably more extensive (Fig. 11). About each central vein is an area, implicating about one-third of the space from central vein to portal space, in which liver cells are replaced by a loose vascular tissue containing numer-

ous mononuclear cells. In immediate contact with the vein these cells are small and very numerous, whereas at a greater distance they are larger and contain abundant pigment. Newly formed bile ducts in moderate numbers occur within and at the margin of the tissue. The liver cells which are well preserved and exhibit little infiltration with fat, are often arranged in tubular columns with nuclei near either margin of the columns.

In the animal (Chlor. xxxiii) which for control received repeated intravascular injections of streptococcus, the liver cells exhibit infiltration with fat in moderate quantity. There is no destruction of parenchyma or other noteworthy alteration. In other animals (Chlor. xxviii and xxxvii) which have been repeatedly inoculated with the same strain of Streptococcus pyogenes, no noteworthy hepatic lesion has been produced.

In the following experiment, two animals have received a single large dose of chloroform; one has been allowed to recover, whereas the other has received repeated intravenous injections of Streptococcus pyogenes.

A dog (Chlor. xxxix) weighing 4850 grams has received by mouth 15 c.c. of chloroform. On the following day it has appeared sick, but has quickly recovered, losing at the end of two days 100 grams of body weight. On the fifteenth day of the experiment the animal has been killed. The liver is not enlarged; its surface is smooth, and its color and texture are those of the normal organ.

A dog (Chlor. xxxviii) weighing 6000 grams has received by mouth 15 c.c. of chloroform; almost immediately 0.5 c.c. of a bouillon culture of Streptococcus pyogenes has been injected into the jugular vein. During the next two days the animal has been very sick and has lost 450 grams of body weight. On the fourth, sixth, eighth, and twelfth days of the experiment it has received 0.25 c.c. of a twenty-four-hour bouillon culture of streptococcus; it has died on the fifteenth day. The liver is much enlarged with homogeneous deep red color and turgid appearance. In places upon the surface is a thin layer of fibrin. Lobulation is not definable on the deep red surface.

The liver of the animal (Chlor. xxxix) which has received two weeks before its death a single large dose of chloroform exhibits

little change (Fig. 14). The liver cells contain fine droplets of fat, but are otherwise normal; there is no increase of interstitial tissue.

In the liver of the animal (Chlor. xxxviii) which has received the same quantity of chloroform, followed by repeated intravascular inoculation with streptococci (Fig. 13), a conspicuous mass of loose-meshed connective tissue replaces the hepatic parenchyma about each central vein and at times extending from one to another central

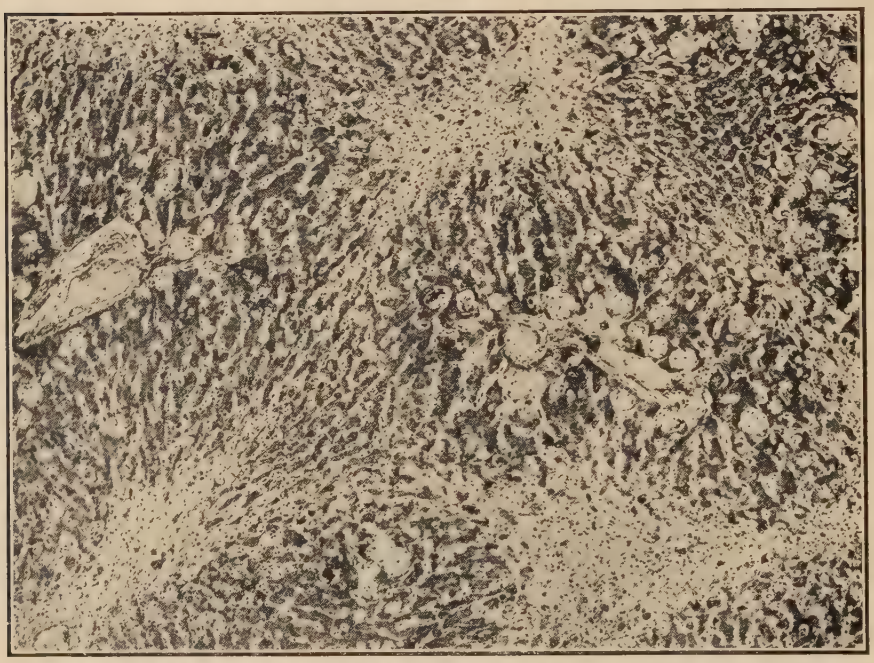

Fig. 13.—Photograph showing the liver of a dog (Chlor. xxxviii) which has received a single large dose of chloroform followed by intravenous inoculation with streptococci. Interstitial tissue replaces the parenchyma in the centre of each lobule; there is enormous dilatation of capillaries about the portal spaces.

vein, maps out islands of parenchyma, each with a portal space in its centre. The new interstitial tissue is rich in cells and contains abundant blood, some of which has apparently escaped from the vessels. The tissue contains many cells resembling fibroblasts, but new formation of intercellular substance is not evident. In immediate contact with portal spaces and in the adjacent parenchyma are widely dilated bloodvessels, at times collected into groups resembling

angiomata. Such dilated vessels, which are apparently preexisting capillaries which have undergone immense dilatation, do not occur in the central part of the lobule. It is possible that this localized dilatation of capillaries is referable to an increased pressure in the domain of the hepatic artery, dilating the capillaries at the junction

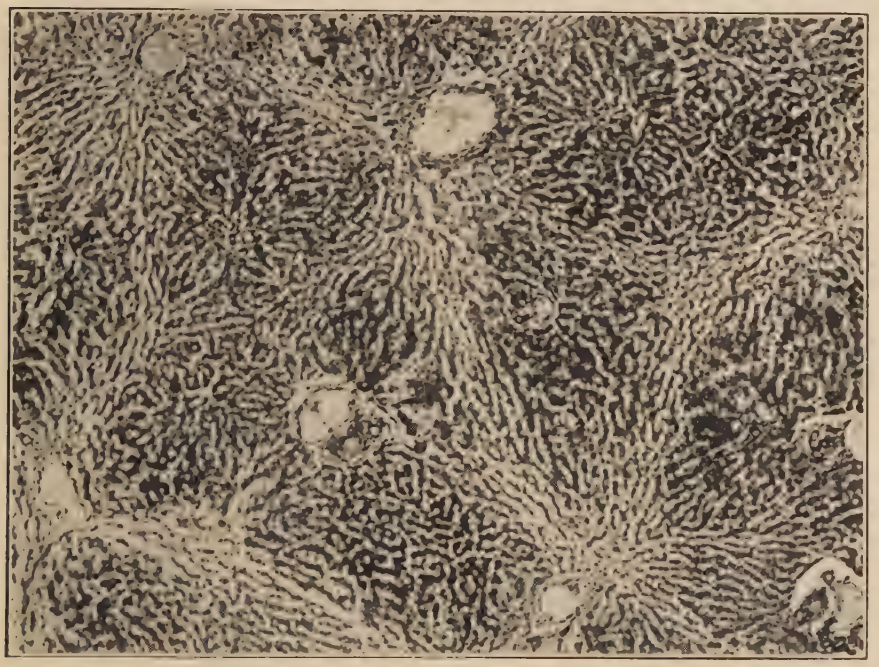

FIG. 14.—Photograph showing the liver of a dog (Chlor. xxxix) which has received a single large dose of chloroform (corresponding with that administered to Dog Chlor. xxxviii). The liver shows no noteworthy change. For comparison with the foregoing figure.

of arterial with portal vascular system, but direct evidence in favor of this suggestion has not been obtained.

The experiment shows that infection with streptococcus retards the regeneration of hepatic parenchyma after destruction caused by chloroform.

The experiments in which chloroform has been administered interruptedly during a considerable period show that chloroform is capable of causing cirrhosis so advanced that the portal circulation is obstructed. Dilatation of superficial abdomen veins is recog-

nizable during life; venous engorgement in the portal domain, œdema of the pancreas, and moderate accumulation of ascitic fluid have accompanied the hepatic lesion. The relation of necrosis of the liver to newgrowth of interstitial tissue is obvious in these experiments, for both occur primarily in contact with the central vein of the lobule. Proliferation of bile ducts occurs and newly formed tubules may appear near the centre of the lobule, often separated from the ducts of the portal space by a broad zone of relatively normal parenchyma.

Bacterial infection in association with intoxication by hepatic poisons such as chloroform and phosphorus have reproduced the peculiar mid-zonal necrosis of the liver which, in man, is almost invariably found in association with acute bacterial infection. Neither chloroform nor phosphorus alone produces this lesion, but either, when associated with the bacteria which have been employed, may produce it.

The same combination of bacteria and poison, doubtless acting with greater intensity, reproduces a lesion which closely resembles acute yellow atrophy in man. There is necrosis and hemorrhage; accumulation of wandering cells and formation of connective tissue replacing parenchymatous elements quickly follows. The regenerative change both of parenchyma and of interstitial tissue observable in man occur in the experimental lesion. New formation of bile ducts is a conspicuous feature of these regenerative changes.

The experiments have shown that bacteria in association with toxic substances such as chloroform and phosphorus having a special affinity for the liver may produce changes which neither the poison nor the bacteria can cause when acting alone. The possibility that disturbances of metabolism in man may produce changes in the liver similar to those caused by such poisons is well illustrated by the toxemia of pregnancy, in which persistent vomiting is associated with central necrosis of the hepatic lobule similar to that caused by chloroform. The experiments show that the activity of an hepatic poison may be so intensified by bacterial infection that a quantity of the poison which alone produces little change may, in combination with the bacteria (Bacillus coli and Streptococcus pyogenes have been employed), cause destruction of almost the entire hepatic paren-

chyma. Bacteria, *e. g.*, colon bacillus, which have little pathogenicity for the normal animal, are virulent for the animal whose liver has been injured by chloroform or phosphorus. It is probable that those instances of acute yellow atrophy which accompany infection with Streptococcus pyogenes are dependent upon some disturbance of metabolism or other form of intoxication which has rendered the liver unusually susceptible.

The experiments furthermore show that bacterial infection can influence and even determine the development of cirrhosis of the liver. Degenerative changes which usually undergo rapid repair may cause sclerosis when combined with bacterial infection. Whereas cirrhosis may be caused by chloroform without bacterial inoculation, introduction of bacteria hastens the progress of the chronic change. The poison in large quantity rapidly causes death, but a much smaller quantity in association with a relatively non-pathogenic microörganism produces a lesion with which recovery is possible. Such insults repeated at intervals produce the chronic changes of cirrhosis. By administration of chloroform, accompanied by intravenous inoculation with Bacillus coli, it has been possible to produce advanced hepatic cirrhosis accompanied by active new formation of bile ducts within a period of twenty-three days.

DISCUSSION.

Dr. S. J. Meltzer: The results obtained by Dr. Opie are significant from a scientific as well as from a practical point of view. I should like to offer an interpretation. Dr. Opie tells us that the injuries produced by chloroform alone return to normal, but if a bacterial infection be added the injuries heal under formation of connective tissue. Some years ago Dr. Cheesman and I presented a paper before this Association on the effects of intravenous injection of bacteria. When typhoid or colon bacilli or streptococci were injected in normal animals they disappeared from the circulation in a short time. When, however, previous to the injection a slight lesion was produced in the spleen, the liver or the uterus, the injected microörganisms settled in the injured place and began to develop there. In Dr. Opie's experiments the chloroform caused an injury to the liver, which offered a focus for the subsequently injected bacteria, where they could develop and destroy the tissue; hence the healing by scar formation.

Dr. William H. Welch: The results obtained by Dr. Opie are, of course, extremely interesting to pathologists as bearing on the etiology and pathogenesis of some cases of hepatic cirrhosis. As he has stated, Dr. B—— found in the laboratory that the colon bacilli, for instance, disappeared promptly; but, if anything occurs which causes these bacilli to remain in the liver, there is produced usually a necrosis. At that time, however, they were not familiar with the finer points and types of necrosis; there occurred small focal necroses. However, when the colon bacilli disappeared from the liver and appeared in the gall-bladder, they could survive there indefinitely; thus, the gall-bladder became a bacillus carrier. The typhus bacillus may remain for months in the gall-bladder, or for an indefinite time. This is another instance of a bacillus carrier. Experimental work upon cirrhosis of the liver has hitherto been very unsatisfactory, particularly with alcohol. I have never succeeded in producing cirrhosis of the liver experimentally with alcohol. I think that Dr. Opie's inferences are correct. You have, as he says, something which produces a damage to the liver causing an actual death; but with the liver's enormous power to regenerate after liver abscess does not lead to cirrhosis of the liver. In order to get cirrhosis of this organ we must inhibit this regenerative power. A combination of the action of toxins with something which prevents this regenerative power may give the real explanation of the cause of cirrhosis of the liver. Of course, the type of cirrhosis which we get experimentally is not the same or exactly like what is found naturally. But I believe his contribution is of vast importance and a great aid in the understanding of cirrhosis of the liver in the sense that there must be something which inhibits regeneration.

Another point of interest pertains to the source of the newly formed bile ducts. They really come from the liver cells; this looks as though this had been conclusively demonstrated. The newly formed bile ducts are really the result of a metaplasia of bile duct epithelium.

I have been very much interested in the relation of this experimental work by Dr. Opie and the investigations he has made on the formation of cirrhosis of the liver that he has brought out by experimentation.

Dr. A. S. Warthin: I should like to ask Dr. Opie if he would extend the views he has just given to apply to the following case. A woman who was seven months pregnant, and intensely icteric, was operated on for gallstones and died soon after the operation. Portions of the liver were immediately taken from the body and were fixed; the remainder of the liver was left in a warm room for about six hours and then more of it fixed. In these portions of the liver the microscopic picture of acute yellow atrophy appeared. There was a central necrosis of the lobules all through the liver, and colonies of colon bacilli were found in the sublobular veins; whereas in the tissues taken from the body itself and immediately fixed no such microscopic changes were found at all. The rapid development of a central necrosis of the liver lobules *after* its removal from the body shows that the microscopic picture of acute

yellow atrophy, eclampsia, or chloroform poisoning may develop post mortem under certain conditions, and that such autolyses of the liver cannot always be regarded as having occurred before death. In this case we have the two factors of icterus and pregnancy existing before death and a possible post-mortem growth of colon bacilli as the explanation of such characteristic central necroses developing after death.

Dr. William G. MacCallum: Dr. Opie's work adds an important fact to those already available for our explanation of cirrhosis of the liver—the intense destructive effect of the combination of bacterial with other poisons. It becomes evident that in addition to the processes of destruction which affect the liver cells and the bile ducts, there is not only repair in these tissues, but also an excessive participation on the part of the connective tissues in the attempts at healing. I myself have never seen anything which would lead me to believe that this is primary and that compression of the liver cells by contracting scar tissue could produce the characteristic features of cirrhosis of the liver—rather I feel convinced that the crowded bile ducts are added to by new formed ones sprouting from the old by a process of mitosis. Indeed, there seems to be no reason why the proliferation of remnants of liver tissue should not produce bile-duct-like structures, even at a distance from the preëxisting ducts.

Dr. E. L. Opie: These experiments clearly illustrate the relationship between connective tissue formation and necrosis. Necrosis occurs only in the centre of the lobule, and new formation of connective tissue in animals in which cirrhosis has an opportunity to occur is in the central part. Connective tissue in the periphery of the lobule is not stimulated to proliferate. The relation of newly formed bile ducts to the centre of the lobule is best seen in specimens in which the lesions are not advanced. Newly formed bile ducts are frequently separated by wide areas of normal hepatic tissue from the portal spaces; in such instances there is little probability that they arise from the bile ducts of the portal spaces.

METABOLISM IN DIABETES MELLITUS.[1]

By F. G. BENEDICT, Ph.D., and E. P. JOSLIN, M.D.,
BOSTON.

The metabolism of thirteen patients representing various types of diabetes has been studied at the Nutrition Laboratory of the Carnegie Institution in Boston. The patients remained in the chair and bed calorimeters for intervals of four to six hours. Experiments of fifteen minutes' duration were also made with the respiration apparatus. The majority of the experiments followed a fast of fourteen hours, and the patients remained fasting during the experiments; upon other occasions immediately preceding the experiment they ate a considerable quantity of protein or carbohydrate.

The experiments show an increase in the total metabolism of these thirteen diabetic patients in the bed and chair calorimeters and respiration apparatus, as compared with normal individuals studied under similar conditions. The increase in oxygen absorption was 16 to 21 per cent., of heat elimination, 15 per cent., and the carbonic acid eliminated rose 6 to 7 per cent. In general, the severer the case of diabetes, the greater the metabolism.

The increased metabolism cannot be accounted for by the specific dynamic action of the extra quantity of protein metabolized by these diabetic patients. Other sources of error are presented and answered. Changes in body weight in diabetes are illustrated, and evidence is offered which appears to show that the metabolism of diabetic patients is not proportional to their original body weight.

Dextrose nitrogen ratios are discussed. An exact determination of the dextrose nitrogen ratio is only possible in patients who have

[1] This paper appears in full as Publication No. 136, Carnegie Institution, of Washington, D. C., 1910.

fasted for some time. Although these estimations may be of some prognostic value, the period of fasting which is necessary for their determination in severe cases of diabetes may be at times dangerous, and from our experience we advise great caution in the use of this method for the determination of the prognosis.

The average respiratory quotient was 0.73 in the severe cases, and this would represent the calculated fat protein metabolism.

Evaporization of water from the lungs and skin did not appear to be less than normal.

Under the conditions of the few experiments in which the ingestion of carbohydrates was studied, no material alteration in the metabolism as a whole in the severe cases was observed, but we will not deny the possibility that in further investigations a change in the metabolism may be found. Such investigations we have in view. On the other hand, the ingestion of large quantities of protein resulted in a marked increase in the total metabolism as measured by the three factors, oxygen consumption, heat elimination and carbon-dioxide excretion.

The result of the experiments upon diabetic patients in the calorimeter suggests several practical considerations.

Diabetic patients require considerable quantities of food. One must be careful not to restrict the diet to an extreme degree. Vegetable and starvation days should be carried out with much caution. It is questionable whether it is safe to make patients sugar free by starvation when the diabetes is of great severity and the previous diet has been low in carbohydrates for a long time.

The waste of heat should be prevented and each calorie conserved. Exposure should be avoided and exercise carefully controlled. One might even consider the prevention of loss of energy expended in warming water which is drunk to the temperature of the body, which is the temperature at which it leaves the body as urine, and thus effect a saving of 75 calories more or less.

The value of protein in the diet of diabetic patients requires renewed study.

A respiratory quotient of 0.74 (or above), if constantly found by reliable methods, is a good prognostic sign, and its value may be equal to prolonged diatetic and urinary tests.

The body weight in diabetic patients is a most variable factor, and this should be always borne in mind in estimating the results of treatment.

Many new problems are admirably adapted for investigation by experiments with the calorimeter upon diabetic patients.

DISCUSSION.

Dr. Magnus Levy, Berlin, Germany: I welcome the communication of Drs. Benedict and Joslin, for it furnishes us with a mass of excellently worked-up material. The large number of patients examined renders us independent of accidents which might occur with a single case. Personally, I have much satisfaction in the fact that many of the views which I have expressed upon these questions now find confirmation in these new experiments. I have had an opportunity to examine and discuss in detail a considerable proportion of the results obtained, and I am glad to state, after this preliminary study, that I agree with most of the conclusions which the gentlemen have drawn from their results.

The experiment gives us quite a complete picture of what takes place in the ordinary course of severe diabetes. But I would call attention to the point that in each case of diabetes periods may occur in which quite another condition may exist, and also that even individual cases may be found which may differ essentially from what has been here noted.

The vaporization of water from the skin which, in these experiments, remained about normal, can sometimes fall to 100 c.c. This takes place if a patient with unregulated diet excretes normal quantities of sugar, and water is lost from the body. In this event the skin is so unusually dried up that only a minimum amount of vaporization takes place. If such a patient is quickly placed upon the strictest sort of diet, he often gains, in the course of two or three days, two, three, and even four kilos in weight, which represents a re-accumulation of fluid previously lost, and not a gain of flesh or fat.

Naunyn has called attention to the fact that many a diabetic can get along for weeks with very small quantities of food, amounting to only 1500 to 1600 calories daily, and even upon this diet add many kilos in weight. This implies that the exchange of energy in these patients is essentially less than that of normal individuals. On the other hand, patients are occasionally met with whose metabolism exceeds the normal measure to a very unusual degree. Up to the present time these conjectures have been based essentially upon clinical obser-

vations. For an increase of our knowledge along these lines, and for a confirmation of them, further carefully planned experiments in the respiration calorimeter are necessary. I cannot enter here into details, but refer to the discussion of these topics which I took up in a more thorough manner in the Cartwright Lectures, which I gave last month in New York. To arrive at a more accurate knowledge on these subjects, both those already surmised by me, and those variations among diabetics alluded to above, further carefully arranged experiments are necessary, and I am confident that these experiments will be carried through on a larger scale, and with the well-known carefulness of the gentlemen presenting this paper.

I consider it an especial proof of the careful conduct of the experiments that the respiratory quotients remained about 0.73, and almost never fall below 0.68. This corresponds quite closely to the theoretically calculated values. Earlier experimenters have frequently found far lower values, and these I have always surely considered to have been based on insufficient analyses.

Dr. Theodore C. Janeway: This Association is very fortunate in having presented to it such epoch-making work in the study of diabetes. No such work, with its accurate and conclusive results, has ever been placed before any association in the world. No opportunity for doing such work has previously existed comparable to that which Dr. Benedict, of Boston, has. It was fortunate, as Dr. Benedict himself stated before sailing for Europe, that he had the coöperation and assistance of a man like Dr. Joslin to help him on the pathological side. One would hesitate, however, to put to practical use all the conclusions drawn, particularly as regards increasing the total amount of food. As has already been stated, in diabetes there are periods in which there is a marked increase in carbohydrate tolerance, and yet the disease may again pursue a rapid course. I hope Dr. Joslin may have the opportunity of making observations of patients during the different phases of tolerance in order to determine if what has been observed holds good throughout the course of the disease.

The question of how much protein to feed is of great practical importance. All of us believe that it is second only to the quantitative limitation of the carbohydrates and, in the severer cases, may be of even higher importance. The results shown inform us that individual cases may retain power to obtain some energy from carbohydrate which fails to be had from the proteins. A statement has been made by Falta that human diabetics can always be made to store nitrogen easily. That is not so. Diabetics will sometimes lose in spite of all you can do. The increase in total metabolism in some of Dr. Joslin's cases shows clearly that you cannot expect all diabetics to store nitrogen.

One should be very cautious in regard to accepting gain in weight as an index of improvement in diabetes. In many cases this apparent improvement occurs for a time and is due to a difference in the water content of the body. A diabetic may be getting along with very small quantities of food and yet gain weight, because he stores water. I have frequently seen a sharp gain in weight

which could not be interpreted as due to any improvement in the patient's condition, but to the retention of water, as on green days. However, this may be a very valuable thing in itself. Diabetics often need to retain water. When there is a marked increase in the excretion of urine, then there will be a loss of this water from the tissues and rapid loss of weight.

Dr. A. E. Taylor: Dr. Joslin will permit me to recall that every postulation of a state of suboxidation in medicine has been discredited on investigation. The history of the hypothesis of suboxidation in the essential anemiæ is an illustration in point. It is quite certain that the results of these analyses of Dr. Joslin are correct. A calculation of the date in the literature bearing on diabetes in the depancreatized dog will convince one that excessive rather than subnormal oxidation occurs in the disease.

While I do not question the result and am certain it is correct, I do not feel that a starvation period of fourteen hours is prolonged enough to form the basis of wholly reliable experimentation. Experimental work on normal human beings has taught me that in some individuals the processes of urinary elimination are not completed within fourteen hours after the ingestion of the evening meal; and since these processes may run parallel to the processes of digestion—in particular those of the digestion of protein that are attended by a rise in the curve of heat production—a respiration experiment undertaken fourteen hours after the ingestion of food might yield a spurious result.

Dr. Joslin: Dr. Taylor will be glad to know that the normal individuals used for comparison were under exactly the same conditions as the diabetic. The diabetic had his last meal at six o'clock the previous night and at eight o'clock the next morning went into the calorimeter and remained in it until between twelve and two o'clock. The treatment of the normal individual and the diabetic was exactly the same. Our observations, therefore, began about fourteen hours after the last meal and ended from eighteen to twenty hours after the last meal. The diet of the diabetic patient was controlled and was frequently constant for some period before the experiments. When the paper is published in full, the diet of the patient over a period of months will appear in detail.

The diabetic did not take an excessive quantity of food. The nitrogen in the diet was controlled from beginning to the end. Whereas the nitrogen excretion of the control cases was from 10 to 12 grams per day, in the diabetics it was from 11 to 13 grams per day. The nitrogen was kept purposely within normal limits.

The question of the body weight interested us very much, and I can only emphasize what I have said before, that we feel that great caution should be exercised in deciding upon the progress of these cases, from the body weight alone.

We are looking for odd periods when the metabolism will be different from the general average of our cases, but thus far such periods have not occurred. One of our patients has been under observation for one and a half years; others, for periods of six months. We shall follow up these patients as long as possible, and if peculiar features occur in their metabolism they will be reported. That is an essential part of the work.

DIGESTIVE OR ALIMENTARY HYPERSECRETION OF GASTRIC JUICE.

By JULIUS FRIEDENWALD, M.D.,
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Digestive or alimentary hypersecretion is a condition in which abnormally large amounts of gastric secretion are obtained after the introduction of an ordinary test meal, although the fasting stomach contains but a few cubic centimeters of juice. The latter finding distinguishes this condition from continuous hypersecretion. This disorder was first described by Straus,[1] who pointed out that in some forms of hyperacidity relatively large quantities of a thin, watery, gastric secretion were obtained one hour after a test breakfast. He attributed this condition to the disturbance of the starch digestion, on the ground that the undissolved starch acted as a stimulant to the further secretion of hydrochloric acid. Zweig and Calvo[2] investigated this condition more fully. They employed the Sahli test meal as a means of distinguishing it from other conditions and designated it "Alimentary Hypersecretion." They differentiated alimentary hypersecretion from the larval hyperacidity described by Straus and by Schüler,[3] characterized by the following symptoms: (1) The formation of amidulin. (2) An increased amount of stomach contents. (3) A lowered specific gravity. (4) A lowering of the freezing point.

The typical symptoms of hyperacidity are present in larval hyperacidity, and yet the contents removed after the test breakfast reveal a normal percentage of free acid. Straus and Schüler assume that in these cases there is actually a hyperacidity, which is not revealed

[1] Deut. Archiv f. klin. Med., 1896, Band lvi, S. 120.
[2] Archiv f. Verdauungskr., 1903, Band lx, S. 262.
[3] Münch. med. Wochenschrift, 1898.

because the examination of the gastric contents is made an hour after the test breakfast has been taken. It is possible that the increased quantity of acid secreted at first (secretio celer et magna) is soon neutralized by the so-called diluting secretion, so that the amount of acid in the test breakfast is found to be normal or subnormal. Elsner[1] working under the direction of Boas again called attention to this condition, and Boas[2] more recently investigated this question and considers the term digestive gastrosuccorrhea more appropriate than alimentary gastrosuccorrhea. This particular form of increased gastric secretion is dependent upon the act of digestion, in contradistinction to continuous hypersecretion in which the secretion extends beyond the digestive act, and in which considerable amounts of gastric juice are found in the fasting stomach. All of the twelve cases reported by Boas occurred in males; the disease is found in youth as well as in old age. An important symptom is the extreme emaciation, a loss of from ten to fifteen pounds in weight being a rather usual occurrence. This loss of flesh is a most important sign, especially since it appears without the slightest tendency to disturbance of motility of the stomach. The appetite and quantity of food consumed may be normal; occasionally, however, both may be decreased. The great loss in weight must depend upon the loss of gastric secretion. Amylolysis is greatly diminished and constipation is very marked. The subjective signs are of much the same character as those found in nervous dyspepsia. Patients complain of various sensations in the stomach, pressure, fulness, eructations, excessive flow of saliva; occasionally of violent pains; very rarely, if ever, heartburn; often acid eructations. Nausea or vomiting rarely occur. Nervous symptoms are usually present, as headaches, insomnia, etc. A marked splashing sound is observed in the region of the stomach; tender spots, painful to pressure, are not observed; the abdomen is occasionally distended with gas. A diminution in the chlorides and an increase in indican are frequently observed in the urine. This disease is much like atony, and Boas believes that there can be no question but that it has in many instances been mistaken for atony or nervous dyspepsia. In order to determine

[1] Berlin. klin. Wochenschrift, 1904, No. 25, S. 670.
[2] Deut. med. Wochenschrift, 1907, No. 33, S. 135.

the presence of this condition, Boas advises a dry test meal. As bread contains 35.5 per cent. of water, he utilizes Albert cakes, containing but 8.9 per cent. of water. If five Albert cakes are given as a test meal and removed from the stomach at the end of an hour, but a small residue will be recovered under normal conditions. In digestive gastrosuccorrhœa, however, 100 to 200 c.c. of fluid may be obtained. On standing, it forms into two layers, a lower layer slight in amount precipitated to the bottom, and above a clear or slightly cloudy fluid, three or four times as large in amount. On examination the secretion generally shows a total acidity and a percentage of free hydrochloric acid not above and often below normal. Boas found in a large proportion of cases a total acidity of from 40 to 56, and free hydrochloric acid 35 to 45, which indicates that while in this condition there may be no excess in the acid of the gastric secretion, the secretion is greatly increased in quantity. In other words, there is a hypersecretion, but no hyperacidity. The average specific gravity of the gastric juice is 1012. The secretion presents a more or less marked biuret and sugar reaction, while albumin is not present; erythrodextrin, amidulin and also the amylum reactions are usually marked. By means of the dry diet, the diagnosis is made positive. If the bottom layer of the secretion is large, there must be a motor disturbance present at the same time. Boas also investigated the contents of the stomach in the fasting state, and pointed out three distinct types of digestive hypersecretion:

1. A form in which the motor function of the stomach is normal and in which no contents are obtained from the fasting stomach.

2. That type in which more or less acid gastric juice is obtained from the fasting stomach, such as is observed in permanent gastrosuccorrhœa.

3. A type in which the motor function of the stomach is markedly disturbed at the same time.

The symptoms do not point definitely to the condition; the most marked are those of chronic nervous dyspepsia with marked emaciation, succussion in the region of the stomach a considerable length of time after meals, and even after small meals. The symptoms often point to atony; therefore, in order to arrive at an exact diagnosis three forms of examinations must be used:

1. Examination of the fasting stomach.

2. Examination of the gastric contents one hour after the dry test meal.

3. Examination of the gastric contents one hour after a test breakfast.

Zweig[1] has recently again reported his observations in this condition. He attributes the most prominent symptom of the disorder, loss of flesh, not to the loss of gastric juice as pointed out by Boas, but to the fear of eating due to the great discomfort produced by the ingestion of food. He also calls attention to the marked constipation attendant upon this disorder, and also to the fact of the great variability of symptoms, the best of health being enjoyed for weeks, to be followed by days of marked discomfort due often to psychic influences, such as sorrow, excitement, etc. A very frequent symptom is the splashing sound produced over the area of the stomach, which is often considered a sign of atony of the stomach. This sound is really devoid of any diagnostic value regarding this condition. It should, however, attract attention at once to the possibility of a digestive gastrosuccorrhea. Zweig investigated eighteen cases, employing the Sahli method; in the remainder of his cases he utilized the Ewald-Boas test breakfast. He found that under normal conditions the amount of solid sediment is from 40 to 60 per cent. of the total sediment, while in alimentary hypersecretion the amount of solid sediment is always under 30 per cent., while the fluid contents amounts to from 70 to 93 per cent. Zweig also points out that even in those cases in which the total amount of gastric contents is not increased, but in which these relations of the solids to the liquid exist, an alimentary hypersecretion must be assumed. In his investigations Zweig placed the gastric contents into test-tubes graduated in cubic centimeters 20 cm. in length and 3 cm. in diameter, which were contrifugalized and the amount of sediment determined. If the entire quantity of solid sediment after a test breakfast is over 77 c.c., Zweig considers that the alimentary hypersecretion is accompanied by a motor insufficiency.

In his 18 cases, 10 presented a hyperacidity, 2 a subacidity, and

[1] Archiv f. Verdauungskr., 1907, Band xiii, S. 143.

6 a normal acidity. The specific gravity is always reduced; instead of the normal 1015 to 1020, the values are reduced to 1007 to 1012.

The disturbance of starch digestion depends on the degree of hyperacidity. In all cases accompanied by a marked hyperacidity a disturbance of amylolysis with the production of amidulin is observed. In one case of subacidity acchroödextrin was present, in all other cases erythrodextrin was produced. In two cases he noted the passage of an alimentary hypersecretion into a continuous gastrosuccorrhea. In his 18 cases, but 4 were observed in females; 14 in males.

My own observations extend over a series of 14 cases. Of these, there are 12 males and 2 females. The ages vary between eighteen and sixty-four years. The symptoms are largely those of a gastric neurasthenia, consisting of fulness, pressure, distention, eructations, and pains in the region of the stomach, together with occasional attacks of nausea and vomiting, rarely of heartburn, and usually with extreme constipation. In all cases general nervous symptoms are manifested, as lassitude, headache, insomnia, irritability, and depression. A marked feature in our cases is the variability of symptoms; periods of discomfort alternating with unaccountable periods of well being; the periods of discomfort, apparently often being induced by nervous influences, such as shock or anxiety. A symptom present in all instances is the emaciation; a loss of weight of from fifteen to thirty-two pounds was observed in our cases. This is especially striking, as the appetite and amount of nourishment consumed was not abnormally diminished in any instance. Localized areas tender to pressure were observed in only two cases, but were inconstant. A marked succussion sound was detected in all cases long after meals, and even after small meals. Three of our cases were complicated with an enteroptosis; in none was the stomach dilated. The following examinations were made in all instances:

1. Extraction and examination of the gastric contents one hour after taking an Ewald-Boas test breakfast.

2. An examination of the gastric contents made one hour after taking a dry test breakfast.

3. An attempt made to extract and examine the contents from the fasting stomach.

At least three examinations were made in all instances; the average results obtained from each individual being recorded in our tables.

1. *Gastric Contents Extracted After an Ewald-Boas Test Breakfast.* The quantity of contents obtained was always very large, varying between 190 c.c. and 410 c.c. This is always a most striking feature of this condition, and should alone point to the possibility of the existence of an alimentary gastrosuccorrhea. The appearance of the contents was also characteristic, for the most part a very watery secretion with but little sediment. On standing, two layers were formed, a lower layer of solid sediment very slight in amount and above an almost clear fluid layer very much larger in quantity. After centrifugalization, the amount of solid sediment in proportion to the total sediment was constantly under 32 per cent., and even as low as 6 per cent., while the fluid ranged as high as 94 per cent., and was but once as low as 68 per cent. Under normal conditions the proportion of solid to the total sediment varies between 40 and 60 per cent.; this variation, therefore, from the normal, presents another very significant sign of digestive gastrosuccorrhea. The specific gravity of the gastric contents varied between 1005 and 1014, being reduced from the normal values 1015 and 1020. In our 14 cases, 8 presented a hyperacidity, 5 a normal acidity, and 1 a subacidity. In the hyperacidity cases the total acidity ranged between 94 and 70; free hydrochloric acid between 74 and 44; in the normal cases, the total acidity varied between 64 and 42; free HCl, between 42 and 32; in the subacidity case the total acidity was 28; free HCl, 10. The starch digestion depends largely on the degree of acidity. In the hyperacidity cases there was a marked interference with the amylolysis with the formation of amidulin. In the cases with a normal percentage of acid, erythrodextrin was formed; while in the subacidity case, acchroödextrin was obtained.

2. *Gastric Contents Extracted After a Dry Test Breakfast.* Inasmuch as wheat bread contains about 35.5 per cent. of water, the ordinary soda crackers, containing but 6 to 7 per cent. of water, were utilized in place of bread. The contents of the stomach was expressed at the end of one hour. In normal individuals little (5 to 15 c.c.) or no gastric contents can be obtained under these conditions. In our cases of alimentary hypersecretion from 104 c.c. to 220 c.c.

of secretion was obtained without difficulty. The secretion expressed was of a very thin watery appearance with but a small amount of solid residue. On standing it formed into two layers, a lower small layer of solid residue and an upper and larger almost clear fluid layer. On centrifugalizing, the amount of solid sediment in proportion to the total sediment was constantly under 22 per cent., and even as low as 6 per cent.; while the fluid residue was as high as 94 per cent. and never below 78 per cent. The specific gravity of the gastric contents varies between 1005 and 1014. With the dry test meal two of our cases presented a hyperacidity, four a normal acidity, and one a subacidity. In the hyperacidity cases the total acidity varied between 85 and 80, the free hydrochloric acid between 68 and 72. In the normal cases the total acidity ranged between 40 and 58; the free hydrochloric acid between 34 and 46, and in the subacidity case the total acidity was 20, free hydrochloric acid 5. In the hyperacidity cases there was a formation of amidulin; in the cases with a normal percentage of acid, erythodextrin; in the subacidity case, acchroödextrin.

3. *Extraction of Contents from the Fasting Stomach.* This procedure was attempted in all instances. In not one of our cases could more than 10 to 15 c.c. of contents be obtained.

The combination of an alimentary hypersecretion with a continuous gastrosuccorrhea was, however, twice noted by Zweig. Alimentary gastrosuccorrhea is a gastric affection of nervous origin, which is apt to extend over a long period of time, presenting great variability of symptoms, with days and weeks of apparent perfect health giving place suddenly to periods of severe distress. That this disorder is purely a form of gastric neurasthenia is manifested by the fact that when the patient is restored to good health the increased secretion is apt to disappear. This condition occurred in two of our cases, No. 7 and No. 10, in whom after an Ewald-Boas test breakfast the quantity of gastric secretion was reduced to from 30 to 50 c.c., and with a dry meal no secretion could be obtained for a short period of time. On the other hand, Zweig has shown that this affection may pass over into a condition of continuous gastrosuccorrhea if improperly treated. The treatment is largely the treatment of nervous dyspepsia. As most patients have lost much

flesh and strength, the best results are obtained by means of the rest cure. In five of our cases in whom this form of treatment was undertaken excellent results were obtained. Ordinarily the diet should consist of three meals a day, as all food ingested has a tendency to increase the gastric secretion. The nourishment should contain an excess of proteids and fats and a small proportion of carbohydrates. Of the proteids, milk, eggs, and fish are to be preferred, as they do not tend to increase the gastric secretion as much as meat. Fats decrease the acid of the gastric secretion, and are therefore highly recommended; they should be given as butter, cheese, cream, and olive oil. The carbohydrates should only be allowed in the most digestible forms, as vegetables, in purée form, dextrinized flour, and stale bread and toast. The quantity of fluids ingested need not be decreased in this affection. Large quantities of milk and alkaline waters may be taken with benefit. Such food as bouillon, meat extracts, coffee, tea, and alcohol, as well as all acid and spiced foods should be avoided. The alkalies with or without belladonna or its preparations are often serviceable in the treatment of this disorder. It is needless to point out that such measures as hydropathic procedures, massage, etc., which have a tendency to build up and strengthen the nervous system are of great service in the treatment of this affection.

Table of Cases Presenting the Results of the Examination of Gastric Contents Following an Ewald-Boas Test Breakfast.

No.	Name.	Age.	Sex.	Entire quantity expressed.	Total acidity.	Free HCl.	Specific gravity.	Microscopic findings.	Remains per cent.		Amylolysis.
									Solid.	Fluid.	
1	A. F.	23	M	220	64	42	1005	Normal	28	72	Erythrodextrin
2	T. K.	34	M	190	78	64	1008	"	6	94	Amidulin
3	L. S.	42	M	234	88	70	1009	"	14	86	"
4	O. M.	18	M	410	62	46	1012	"	18	82	Erythrodextrin
5	T. P.	47	M	218	82	70	1007	"	12	88	Amidulin
6	F. J.	28	F	298	94	72	1008	"	24	76	"
7	H. N.	53	M	212	60	46	1012	"	26	74	Erythrodextrin
8	J. J.	64	M	325	86	74	1014	"	32	68	Amidulin
9	M. F.	50	M	244	76	62	1006	"	25	75	"
10	K. E.	48	M	350	42	36	1012	Yeast spores	14	86	Erythrodextrin
11	J. S.	59	M	240	74	60	1011	Normal	12	88	Amidulin
12	T. M.	34	F	334	28	10	1007	"	26	74	Achroödextrin
13	S. C.	45	M	248	54	32	1014	"	25	75	Erythrodextrin
14	J. D.	29	M	224	70	44	1008	"	19	71	Amidulin

TABLE OF CASES PRESENTING THE RESULTS OF THE EXAMINATION OF GASTRIC CONTENTS FOLLOWING A DRY TEST BREAKFAST.

No.	Name.	Age	Sex.	Entire quantity expressed.	Total acidity.	Free HCl.	Specific gravity.	Microscopic findings.	Remains per cent.		Amylolysis.
									Solid.	Fluid.	
1	A. F.	23	M	110	45	36	1008	Normal	18	82	Erythrodextrin
2	T. K.	34	M	104	52	44	1005	"	6	94	"
3	L. S.	42	M	123	46	38	1012	"	10	90	"
4	O. M.	18	M	220	42	34	1014	"	12	88	"
5	T. P.	47	M	105	80	72	1006	"	22	78	Amidulin
6	F. J.	28	F	130	85	68	1009	"	20	80	"
7	H. N.	53	M	125	52	44	1014	"	14	86	Erythrodextrin
8	J. J.	64	M	182	58	46	1013	"	16	84	"
9	M. F.	50	M	115	48	38	1009	"	12	88	"
10	K. E.	48	M	125	40	36	1012	Yeast spores	20	80	"
11	J. S.	59	M	154	55	44	1008	Normal	18	82	"
12	T. M.	34	F	205	20	5	1006	"	16	84	Achroödextrin
13	S. C.	45	M	195	44	36	1012	"	14	86	Erythrodextrin
14	J. D.	29	M	184	55	42	1010	"	20	80	"

Abstract of Cases.

CASE I.—A. F., male, aged twenty-three years, has been suffering with nervousness, and gastric disturbance for six years, there were periods of from three to six months in which all discomforts would subside, and the patient would feel perfectly well, until the onset of another attack. The patient complains of nervousness, irritability, insomnia, and headaches, together with occasional attacks of nausea, though never of vomiting, but of distention and flatulency, and of pain in the stomach. He has lost eighteen pounds in weight in the past three months. On examination the patient is found to be sallow and anemic in appearance; nothing abnormal is detected on examination of the abdomen. The gastric contents after an Ewald test breakfast is large, averaging 220 c.c., with a total acidity of 64; free HCl, 0.15 per cent., of a specific gravity of 1005; on centrifugalizing, the proportion of solid to fluid sediment is as 28 to 72; erythrodextrin reaction marked. After a dry test meal of five crackers, the amount of gastric secretion removed averages 110 c.c. in quantity, with a total acidity of 45; free HCl, 0.13 per cent.; of a specific gravity of 1008; the proportion of solid to fluid sediment is as 18 to 82; marked erythrodextrin reaction. Under a rest cure the patient gradually improved in health, and was free of all distress at the end of ten weeks.

CASE II.—T. K., male, aged thirty-four years, complains of gastric distress for over three years prior to this period; he had had a nervous breakdown which prevented him from following his regular occupation for six months. The symptoms now are entirely gastro-intestinal in character, they consist of distention and fulness after meals, occasionally of pain, of eructations, and of marked constipation. At times the patient feels quite well for a short period of time, when any undue exertion, emotion, or error in diet will induce a similar attack.

He believes that business worry is the direct cause of the present attack. The patient has lost twenty-five pounds in weight. On physical examination nothing abnormal can be detected in the patient's condition. The gastric contents removed after an Ewald test breakfast was large in quantity, amounting to 190 c.c.; total acidity, 78; free HCl, 0.23 per cent.; specific gravity, 1008; the proportion of the solid to the fluid sediment being as 6 to 94; amidulin reaction present. After a dry test meal the gastric contents removed averages 104 c.c.; total acidity, 52; free HCl, 44; specific gravity, 1005; erythrodextrin reaction marked. The patient did well under careful dietetic regulations given him, and continued to improve during the next three months, but he has drifted away from our observation, and the final effect of the treatment cannot be stated.

Case III.—L. S., male, aged forty-two years, has been suffering with his present gastro-intestinal disturbance for the past nine months, though he had had similar attacks three and five years previously. His present symptoms are composed of distention and fulness after meals, nausea, and occasionally vomiting and pain in the stomach; the patient complains of great irritability, nervousness, headaches, and insomnia; he has lost sixteen pounds in weight in the last nine months. Upon examination nothing abnormal is revealed, except a rather marked splashing in the region of the stomach. After an Ewald test breakfast, the amount of gastric contents averages 234 c.c. in amount, with a total acidity of 88; free HCl, 25 per cent.; specific gravity of contents, 1009; the proportion of solid to fluid contents being as 14 to 86; amidulin reaction marked; after a dry test meal the quantity of contents expressed amounted to 123 c.c., with a total acidity of 46; free HCl, 0.13 per cent.; specific gravity, 1012; the proportion of solid to liquid sediment being as 10 to 90; erythrodextrin reaction marked. Under the influence of a carefully regulated diet, proper exercise, and the use of belladona the patient gradually recovered his health and the gastric symptoms disappeared.

Case IV.—O. M., male, aged eighteen years, has had more or less stomach disturbance all his life, with periods of entire relief extending over six to eight months. The symptoms mainly complained of are eructations, nausea and fulness after meals, together with great nervousness. The patient has lost eighteen pounds in weight. On physical examination nothing abnormal can be detected. The entire quantity of gastric juice removed amounted to 410 c.c., with a total acidity of 62; free HCl, 0.16 per cent.; specific gravity, 1012; the proportion of solid to fluid sediment being as 18 to 82; erythrodextrin reaction. After the dry test meal the amount of contents removed is 220 c.c. with a total acidity of 42; free HCl, 0.15 per cent.; specific gravity, 1014; proportion of solid to liquid contents as 12 to 88; erythrodextrin reaction marked. Under a partial rest cure and the use of belladonna with nux vomica, the patient was gradually relieved of his symptoms.

Case V.—T. P., male, aged forty-seven years, after an intense shock was suddenly overtaken with nervousness and gastric distress, there was present marked depression, insomnia, nausea and vomiting of large quantities of fluid

immediately following the meals, and a loss of appetite. He has been suffering three months, and has already lost twenty-five pounds in weight. Physical examination reveals nothing abnormal after an Ewald test breakfast; the quantity of gastric contents averaged 218 c.c., with a total acidity of 80; free HCl, 0.26 per cent.; specific gravity, 1006; proportion of solid to liquid contents as 22 to 78; amidulin reaction present. The patient was entirely relieved of his symptoms by a sojourn at the seashore combined with dietetic and hydropathic treatment.

Case VI.—F. J., female, aged twenty-eight years, has been complaining with indigestion and nervousness for over eight years; at times she would be quite well and free of all distress, when without cause another attack would manifest itself. The attacks last from two or three months, and are characterized by a feeling of exhaustion and nervousness, pressure and fulness in the stomach after meals, and extreme constipation. The patient has lost thirty-two pounds in weight. On physical examination a marked enteroptosis is detected, together with a succussion sound in the region of the stomach. After an Ewald test breakfast the quantity of secretion obtained was 298 c.c., with a total acidity of 94; free HCl, 0.26 per cent.; specific gravity, 1008; the proportion of solid to liquid sediment is as 24 to 76; amidulin reaction present. After a dry test meal 130 c.c. of contents were obtained with a total acidity of 85; free HCl, 0.25 per cent.; specific gravity of 1009; the proportion of solid to liquid sediment is as 20 to 80. The usual dietetic and hydropathic treatments were undertaken in this case; the patient was, however, not relieved of his discomfort.

Case VII.—H. N., male, aged fifty-three years, had been complaining of discomfort in his stomach for the past fifteen years. The disturbances are not always equally severe, and would disappear for months at a time during this period. On physical examination the patient is found very thin, a marked splashing sound can easily be elicited in the region of the stomach. There is marked enteroptosis present; otherwise nothing abnormal is detected. After an Ewald test breakfast 212 c.c. of contents are removed, with a total acidity of 60; free HCl, 0.16 per cent.; specific gravity, 1012; proportion of solid to liquid sediment is as 26 to 74; erythrodextrin reaction marked. After a dry test meal, an average of 125 c.c. of contents was obtained with a total acidity of 52; free HCl, 0.16 per cent.; specific gravity, 1014; proportion of solid to liquid sediment is as 14 to 86; erythrodextrin reaction marked. After a rest cure of six weeks the patient recovered his health entirely, and was completely free from all discomfort. An Ewald test breakfast was given at this time, the quantity of contents obtained was but 30 c.c., with a total acidity of 40; free HCl, 0.12 per cent.; after a dry test meal no secretion could be obtained.

Case VIII.—J. J., male, aged sixty-four years, has been complaining of nausea and vomiting for a year and a half; the vomiting of large quantities immediately after meals has been especially noted by the patient. He has lost twenty-eight pounds in flesh during this time. On physical examination nothing abnormal can be detected. After an Ewald test breakfast 325 c.c. of contents were removed, with a total acidity of 86; free HCl, 0.27 per cent; specific

gravity, 1014; total solid to liquid sediment as 32 to 68; amidulin reaction marked. After a dry test meal an average of 182 c.c. of gastric contents was obtained, with a total acidity of 58; free HCl, 0.17 per cent; specific gravity, 1013; proportion of solid to liquid sediment as 16 to 84. The patient was dieted, and given belladonna and the alkalies, and was somewhat relieved of his discomfort.

Case IX.—M. F., male, aged fifty years, has been suffering with a digestive disturbance accompanied with nervousness for over five years; during none of this time has the patient been able to partake of a general diet, being forced to limit himself to but a very few articles of food; if a liberal diet was indulged in he would become nauseated, have fulness and distention in the region of the stomach, suffer with eructations, and occasionally with heartburn, with headaches, and depression. The patient is always extremely constipated, he has lost fifteen pounds in weight. On physical examination nothing abnormal can be detected. After an Ewald test breakfast an average of 244 c.c. of gastric contents were obtained, with a total acidity of 76; free HCl, 0.22 per cent.; specific gravity of 1006; proportion of solid to liquid sediment as 25 to 75; amidulin reaction marked. After a dry test meal 115 c.c. of contents were obtained; total acidity, 48; free HCl, 0.13 per cent.; specific gravity, 1009; proportion of solid to liquid sediment as 25 to 75; amidulin reaction marked. After a dry test meal 115 c.c. of contents were obtained; total acidity, 48; free HCl, 0.13 per cent.; specific gravity, 1009; proportion of solid to liquid sediment is as 12 to 88, erythrodextrin reaction marked. A rest cure of eight weeks was undertaken; the patient gained forty pounds in weight and was entirely relieved of all of his discomfort.

Case X.—K. E., male, aged forty-eight years, reported that he had been suffering with general neurasthenia for many years; he has only complained with disturbance of his digestion, however, for the past seven months; the symptoms associated with this condition are fulness, distention, and nausea and vomiting of large quantities of clear fluid following his meals. Physical examination reveals nothing abnormal; after an Ewald test breakfast 350 c.c. of contents were removed, with a total acidity of 42; free HCl, 0.13 per cent.; specific gravity, 1012; proportion of solid to liquid sediment is as 14 to 86; erythrodextrin reaction marked. After a dry test meal 125 c.c. of contents were removed, with a total acidity of 40; free HCl, 0.36 per cent.; specific gravity 1012; proportion of solid to liquid sediment is as 20 to 80; erythrodextrin reaction marked. The patient gradually recovered his health. This was accomplished by means of a sojourn in the mountains in connection with the regulation of the diet, and the internal administration of belladonna. An Ewald test meal given three months after the patient recovered revealed the fact that but 50 c.c. of gastric contents could be obtained, with a total acidity of 42; free HCl, 0.11 per cent. The stomach was found completely empty when employing a dry test meal.

Case XI.—J. S., male, aged fifty-nine years, has been suffering with a disturbance of his digestion for three years, his symptoms consisted of extreme constipation, nausea, eructations, and pressure and fulness after meals. The patient is quite nervous, and suffers greatly with insomnia. He has lost twenty-

three pounds in weight. Nothing abnormal can be detected on physical examination. After an Ewald test breakfast 240 c.c. of gastric contents were obtained, with a total acidity of 74; free HCl, 0.21 per cent.; specific gravity, 1011; proportion of solid to liquid sediment is as 12 to 88; amidulin reaction marked. After a dry test meal 154 c.c. of contents were obtained, with a total acidity of 55; free HCl, 0.16 per cent.; specific gravity, 1008; proportion of solid to liquid sediment is as 18 to 82; erythrodextrin reaction present. The patient was entirely relieved of his discomfort by means of a rest cure extending over six weeks.

Case XII.—T. M., female, aged thirty-four years, has been suffering with indigestion for ten years; she has lost much flesh, thirty pounds in the past three years, and complains much of nausea, pressure, and fulness after meals, eructations, and occasionally of vomiting and of extreme constipation. On physical examination nothing but a marked gastroptosis can be detected. After an Ewald test breakfast 334 c.c. of contents were obtained, with a total acidity of 28; free HCl, 0.036 per cent.; specific gravity, 1007; proportion of solid to liquid sediment as 26 to 74; acchroödextrin reaction marked; after a dry test meal 205 c.c. of gastric contents were obtained, with a total acidity of 20; free HCl, 0.018 per cent.; specific gravity, 1006; proportion of solid to liquid sediment as 16 to 84; acchroodextrin reaction marked. The patient was given a rest cure extending over a period of five weeks, and was discharged much improved.

Case XIII.—S. C., male, aged forty-five years, has been very nervous for over three years, he is frequently depressed, often excitable, and suffers very severely with mental depression. During the entire period there has been more or less gastric disturbance, in the form of pressure and fulness after meals, and eructations and nausea. The patient has lost twelve pounds in weight. On physical examination nothing abnormal can be detected. After an Ewald test breakfast an average of 248 c.c. of contents was obtained, with a total acidity of 55; free HCl, 0.11 per cent; specific gravity, 1014; proportion of solid to liquid sediment 25 to 75; erythrodextrin reaction marked; after a dry test meal an average of 195 c.c. of contents was removed, with a total acidity of 44; free HCl, 0.13 per cent.; specific gravity, 1012; proportion of solid to liquid sediment as 14 to 86; erythrodextrin reaction marked. The patient was entirely relieved of this discomfort by carefully regulating his diet, mode of life, and by the administration of eumydrin.

Case XIV.—J. D., male, aged twenty-nine years, has been suffering with indigestion for over six years. At times he would apparently be perfectly well, but the slightest excitement or worry would occasion much gastric distress. The patient complains of nausea, fulness after meals, and occasional heartburn, together with headaches, insomnia, and great irritability. On physical examination nothing abnormal can be detected. The patient has lost twenty-two pounds in weight. After an Ewald test breakfast an average of 22 c.c. of contents was obtained, with a total acidity of 700; free HCl, 0.16 per cent.; specific gravity, 1008; proportion of solid to fluid sediment as 19 to 81; amidulin reaction present.

After a dry test meal an average of 184 c.c. of contents was removed, with a total acidity of 55; free HCl, 0.15 per cent.; specific gravity, 1010; total solid to fluid sediment as 20 to 80; erythrodextrin reaction marked. The treatment of this patient consisted of a carefully regulated diet, exercise, baths, and the administration of belladonna. He was not however, benefited.

DISCUSSION.

Dr. Bertram W. Sippy: You all, no doubt, know that the expression alimentary hypersecretion does not date back very far. As to whether the condition deserves the term remains to be seen and for future experience to determine. An essential clinical manifestation is the presence in the stomach of an abnormally large quantity of the digestive juices, together with the food taken in with the test meal or with the ordinary food. Under normal conditions, in the morning the stomach is empty. When food is introduced, the gastric juice is poured out. After a test breakfast of 60 grams of bread, from 50 to 100 c.c. of liquid food and the gastric juice secreted can be obtained. In this condition a larger quantity is poured out. The motility of the stomach must be interfered with; it may be normal, it may be excessive, or, as more frequently found, there is delayed motility. As pointed out, the secretion may be normal in character. The acid may be normal, it may be subnormal, or it may be above normal in acidity. What are the factors which influence this? There are a number of them. First, there is the increased activity of the glands, when they will pour out a larger quantity of material than they do normally. Then again, the quantity of material aspirated by the individual may not represent the total quantity removed. There are a number of factors which influence the motility and the material found in the stomach. Personally, I have not found the condition very rare, but it is found in people even well nourished. It seems to me that this complex symptom is somewhat interwoven and dependent upon so many factors, such as sensitiveness of the nerves, and the varying motility of the stomach, and perhaps, after all, it may not deserve a separate place, and may not deserve to be mentioned as a particular or definite disease entity.

Dr. Friedenwald: I think the condition must be a form of gastric neurosis, or gastric neurasthenia. It is a fact that the condition disappears when the patients are in better condition. I do not think we can class this as a separate disease, but must place it as a form of gastric neurosis.

CLINICAL EXPERIENCES WITH THE CAMMIDGE REACTION.

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The first work of any considerable extent on the Cammidge reaction in the laboratory of St. Mary's Hospital was that done by Balfour two years ago on 80 cases, following closely Mr. Cammidge's technique. This was very discouraging in results, and was given up largely because "positive" reactions were obtained frequently on apparently normal individuals.

The examinations were resumed by Pilcher in May, 1909, principally on cases showing more or less symptoms of pancreatic involvement. An effort was made to improve the technique by running parallel tests of hydrolized specimens. The cases were studied clinically by Pilcher at the time of making the tests, after the manner described by Mr. Cammidge. They were also seen by Pilcher at operation. The results, which have been published elsewhere,[1] appeared, on their face, to warrant further study of the test as an aid to clinical diagnosis. Thus, of 62 patients at operation showing involvement of the pancreas, 50 gave more or less "positive" reactions; of 50 cases showing at operation no pancreatic involvement, 7 gave more or less "positive" reactions; and of 25 "well" individuals, 1 gave a "positive" reaction. There was a feeling on the laboratory staff, however, that there were great possi-

[1] Annals of Surgery, 1901, li, 89 to 109.

bilities of error in this method of working, not only owing to the indefiniteness of what actually constituted a reaction—due to great variation in color changes, amount of precipitate, type of crystals, relation of controls, etc.—but also to the difficulty of eliminating bias in judgment when the laboratory technician was familiar with the clinical history of the case under consideration.

Willis and McGrath, therefore, took up the study along with Pilcher, five months ago, seeking first to attain a uniform technique; second, to analyze the types of reaction; and third, to eliminate the personal equation by having the end reactions classified by one (Pilcher) who knew nothing of the patient.

The cases were clinically of four classes: (1) Cases shown at operation or autopsy to have involvement of pancreas; (2) cases (with abdominal or pelvic lesions) which at operation or autopsy were shown to have no involvement of the pancreas; (3) sick individuals, in whom the pancreas was not examined; and (4) apparently well individuals.

Technique. The specimens of urine were twenty-four-hour, or mixed evening and morning collections. These were sent to the laboratory in well-stopped bottles immediately after the last portion of the specimen was collected. The specific gravities and reactions were taken. The specimens were then filtered through double filter papers into two beakers, graduated for 40 c.c., and 5 c.c. taken to test for albumin and sugar tests. For the latter, two parts of urine to one of Fehling's solution was used, heating both separately, and then pouring together and allowing to stand.

When a trace of albumin was found, the specimens were acidified with dilute acetic acid, boiled and refiltered.

If the specimen was alkaline (very few), it was acidified with dilute acetic acid.

In making the Cammidge tests proper, all glassware was thoroughly rinsed, and all filter papers well moistened with distilled water. The two 40 c.c. samples of each urine were numbered. To the specimen to be hydrolized was added 2 c.c. chemically pure HCl, specific gravity 1.20 Grasselli. The specimen was gently boiled on the sand bath for ten minutes, with recondensing funnels in place, then transferred into racks to cool in running water. At

this point, when necessary (seldom), distilled water was added to bring the amount up to 40 c.c. Eight grains of pure lead carbonate (Mallinckrodt's) was slowly added to the specimen, which was thoroughly shaken, and was then allowed to stand five or ten minutes for completion of neutralization. It was passed through double, moist filter papers until perfectly clear. The unhydrolized control without previous preparation was from this point run parallel to the hydrolized. Eight grams of pure tribasic lead acetate (Merck) were added slowly to each specimen, which was then well shaken and allowed to stand from ten to fifteen minutes, and then filtered through double moist filter papers until clear. To each 4 grams pure sodium sulphate (Mallinckrodt) were now added, and the specimens brought to a boil on a sand bath, then cooled in running tap water, and filtered through moistened filter paper. To 10 c.c. of the clear filtrate were added successively 1 c.c. 50 per cent. acetic acid, 7 c.c. of distilled water, 2 grams pure sodium acetate (Mallinckrodt) and 0.8 gram phenylhydrazine hydrochlorate (Merck). The specimens were then boiled for ten minutes on the sand bath. Lastly, the specimens were filtered hot, through filter paper moistened with hot water, into test-tubes. Owing to the use of funnel recondensers, the final amounts were uniformly approximately 15 c.c. The tubes were then set aside at a temperature of about 5° C.

For accuracy of results and convenience in handling large numbers of specimens at once, tall beaker glasses (capacity, 170 c.c.; height, 11 cm.; diameter at top, 5 cm.) were used. A copper water bath (64 cm. in length, 33 cm. wide, 6 cm. deep), containing in cover 32 circular apertures (5 cm. in diameter), was used for cooling the solutions in beakers. A reinforced sheet-iron pan with a wire rack cover was used for a sand bath, and gave very uniform heating. From eight to fifteen specimens (*i. e.*, 16 to 30 tests) were carried through at one time by two men working together, one analyzing the specimens to be hydrolized and the other the controls. To facilitate the work, four sets of glassware were prepared in advance. All chemicals were carefully weighed in sets at the same time. When once the analyses were begun they were pushed to completion as rapidly as possible, it usually requiring about three hours to complete a day's tests. In addition to the above, no pains were spared

to make the tests as uniform as possible, even in the most minute detail.

Preliminary Tests. 1. *Sugar.*

In doing the Fehling's test for sugar, a careful record of the colors was kept after the tubes had stood several hours, and three groups adopted:

1. Bluish color—48 tests, 22 of which in the Cammidge test had some form of crystal in either or both of the hydrolized and unhydrolized specimens. Thirteen of the 22 crystalline end reactions were "positive" Cammidge reactions.

2. Greenish color—252 tests, 197 of which in the Cammidge test had some form of crystal in either or both of the hydrolized and unhydrolized specimens. Seventy-four of the 197 crystalline end reactions were "positive" Cammidge reactions.

3. Reddish color—206 tests, 188 of which in the Cammidge test had some form of crystal in either or both of the hydrolized and unhydrolized specimens. Seventy-four of the 188 crystalline end reactions were "positive" Cammidge reactions.

There were 23 urines which gave Fehling's reaction for sugar, 7 of which gave positive Cammidge crystals. A number of the sugar specimens were fermented for twenty-four hours with yeast, and in no case was a crystal obtained subsequently by Cammidge test. A number of urines (same specimens) that had given what was considered most typically "positive" Cammidge reactions were fermented with yeast for twenty-four hours, and subsequently tested for Cammidge crystals. None whatsoever found.

2. *Specific Gravity.*

The apparent relationship of the specific gravity and the Cammidge end reactions is shown in the following tables:

Specific gravity.	Cases.	Results of Cammidge tests. Positive.	Per cent
1025 to 1039	208	88	42.3
1015 to 1024	239	66	27.6
1001 to 1014	56	12	21.4

As soon as the decision as to what constituted a positive end reaction was made to rest solely on the contents of the test-tubes it became evident that the diagnostician with the greatest experience (Pilcher) was frequently unable to decide the value of the various colors, precipitates, and crystals, while others, with less experience, were wholly at sea.

An effort was made, therefore, to analyze and classify the various factors of the end reaction, in order not only to have some uniform nomenclature for recording our observations, but also to determine what valuation should be placed on each variant. With this in view, the following 19 types of hypothetical end reactions were adopted:

Varieties of Reactions in Cammidge's "C" Test. Examination of Tubes Made after Standing Eighteen to Twenty-four Hours at about 5° C.

Variety.	End reaction of HCl specimen.	Diagnostic significance.	End reaction of control.	No. of end reactions each.
1	No change.	Negative.	No change	95
2	Orange color only.	Very doubtful.	No change.	4
4	Amorphous precipitate.	Very doubtful.	No change.	2
5	Amorphous precipitate.	Very doubtful.	Amorphous precipitate.	2
6	Amorphous precipitate.	Very doubtful.	Atypical crystals.	10
7	Atypical crystals.	Doubtful.	No change.	37
8	Atypical crystals.	Doubtful.	Amorphous precipitate.	17
9	Atypical crystals.	Doubtful.	Atypical crystals.	113
10	Typical crystals	"Positive."	No change.	21
11	Typical crystals.	"Positive."	Amorphous precipitate.	7
12	Typical crystals.	"Positive."	Atypical crystals.	72
14	No change.	Negative.	Amorphous precipitate.	6
15	No change.	Negative.	Atypical crystals.	42
16	Orange color.	Doubtful.	Atypical crystals.	1
17	Typical crystals.	Positive.	Typical crystals.	61
18	Atypical crystals.	Negative.	Typical crystals.	11
19	No change.	Negative.	Typical crystals.	3
				504

Two of these types of hypothetical end reactions (3 and 13) were found not to occur, and they have been purposely omitted in the preceding table.

As nearly as can be determined from Mr. Cammidge's somewhat indefinite description of his end reaction, probably four—Nos. 10,

11, 12, and 17—of these types would be (by him) considered positive and the remainder negative.

On this basis, in which we have followed Mr. Cammidge as accurately as possible, the results of our 504 tests may be analyzed as follows:

Group I. Patients with Pancreas Involved.

In this group were 26 cases, 17 of which were examined before operation. Of these, 6 gave positive reactions. Of the same 26 cases examined five days after the operation, 6 were positive, 3 of these having been positive before operation, 1 negative, and 2 not previously examined.

Twenty-four of these cases were examined about the ninth day after operation, and 3 gave positive reactions; these 3 had all been positive at the examination before operation; 1 had been positive on the second test, and the other 2 negative.

Group II. Patients with Pancreas Not Involved.

In this group, containing 74 cases, 26 were examined before operation. Of these, 16 were positive. Five days after operation all 74 were again examined, and 21 were positive. Four of these had been positive before operation, 2 had been negative, and the remaining 15 had not been previously examined. About nine days after operation 69 of these cases were again examined. Seventeen were positive; of these, 5 had been positive before operation, 1 had been negative, and the remaining 11 not examined before operation. Twelve of the 17 cases had been positive five days after operation.

Group III. Sick Persons Whose Pancreas Was Not Examined, but Who Exhibited No Recognizable Symptoms of Pancreatitis.

In this group 207 cases were examined; 73 of these were positive. Of these 73 positives, 17 were goitre cases (44 goitre cases in all

being examined), 9 were appendicitis cases, and the remainder were cases of salpingitis, uterine tumors, etc.

Group IV. Apparently Well Persons (Members of the Hospital Staff).

In this group 17 cases were examined from one to five times each. Of these, 5 were positive.

It will thus be seen that of the 26 patients who were shown to have pancreatitis (Group I), only 9 (35 per cent.) gave a positive reaction, and even of these, 7, in one or more of the series of three tests, gave negative results. Of the 74 sick persons without pancreatitis (Group II), 35 (47 per cent.) gave one or more positive reactions. Of the 207 sick persons who in all probability had no pancreatitis (Group III), 73 (35 per cent.) were positive. Of the 17 well persons, 5 (30 per cent.) were positive.

Summary. From the foregoing it is apparent:

1. That even where the most elaborate care is exercised to follow the technique of Mr. Cammidge's "C" reaction, in the most uniform manner, if knowledge of the clinical histories and other factors of the personal equation be eliminated, the end results, judged by Mr. Cammidge's own criterion, must be considered, as a means of diagnosticating disease of the pancreas, as both valueless and misleading.

2. There is no apparent clinical relationship between disease of the pancreas and any of our various types of end reaction.

3. It does not seem to us that the end reactions are artefacts, but rather that they indicate actual metabolic variations. The relationship of these changes in metabolism to the welfare of the patient is not apparent.

DISCUSSION.

Dr. Francis P. Kinnicutt: Our observations at the Presbyterian Hospital do not permit me to accept Dr. Wilson's conclusions. Our work is done very carefully, and the personal equation is eliminated. The examinations are made by one person, who is an expert chemist and who has no knowledge of the cases. The specimens of urine are simply numbered and sent to the laboratory, and the improved Cammidge test is used in all cases. We have employed it in 126 cases. Positive reactions were obtained in 30, while in the remainder the reactions were negative. The result of our observations up to the present date indicate that while the pancreatic reaction is not pathognomonic of, it is strongly suggestive of inflammatory and destructive lesions of the pancreas, and is of much assistance in diagnosis in association with other clinical evidence of disease of this organ. An analysis of the cases in which the test was employed up to March, 1909, is reported in the *New York Medical Record* of April 10, 1909. Further cases studied since this date up to the present time furnish very similar evidence.

Dr. L. B. Wilson: Our results are far from proving that a positive Cammidge test necessarily indicates a pancreatic lesion. The test was present in many healthy individuals. They were all proved not to have any pancreatic lesions. The proof was as positive as could be made without killing the individuals. There was a larger number of individuals without pancreatic lesions that gave the reaction than there were of individuals who had pancreatic lesions and gave the reaction. In patients with pancreatic lesions the reaction varied greatly. One day they would have a beautiful reaction; while sometime during the next twenty-four hours another specimen would show no reaction. Healthy young men in a boarding house and on a somewhat restricted diet gave no reaction. When, however, they went to a better boarding house, the reaction appeared.

A STUDY OF THE DEVELOPMENT OF THE EPIPHYSES OF THE HAND AND WRIST FOR THE PURPOSE OF CLASSIFYING THE CADETS AT ANNAPOLIS.

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AND

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After the presentation of the paper on "A Study of the Development of the Bones for Determining an Anatomic Index for the Grading of Children up to Thirteen or Fourteen Years," at the Association meeting of May 12, 1909, the Secretary of the Navy requested that a similar index be prepared to aid in grading the naval cadets at Annapolis. A new test for grading the cadets was found to be needed, as some young men apparently ready to enter, by the tests usually made, later were unable to withstand the strain. Others would go along without a breakdown until the four years were nearly up and then break down. For this reason the Government desired some additional means of ascertaining at the beginning whether an individual student would be likely to withstand the strain, both mental and physical, through which he would have to pass.

During the past year work in this direction on young men from fifteen to sixteen up to about twenty years of age has been carried on with the following results. It has been found that the development of the hand and wrist represents so well that of the other epiphyses of the skeleton, that they furnish the best material for the study of epiphyseal development, and, in fact, present an index of the general epiphyseal development from birth to the completion of development at the twentieth or twenty-first year.

PLATE 1

Male, aged seventeen years and two months.

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PLATE 2

Male, aged seventeen years and seven months.

We, therefore, can practically make use of these different stages of epiphyseal development so as to cover two distinct periods, one corresponding to the first thirteen or fourteen years of life and the other from fourteen or fifteen up. The earlier period, as has already been shown in former papers, is determined by the appearance, in succession, of the carpal bones and the epiphyses of the radius and ulna. The later period is represented by the different stages of ossification, leading up to complete union of the epiphyses of the phalanges, metacarpal bones, ulna, and radius. This gradual union of the epiphyses furnishes us with an anatomic index for grading the older individuals, the grading being determined by the different periods at which the union takes place in the above-mentioned epiphyses.

A careful study of the subject shows that those epiphyses, such as, for instance, that of the radius, which appear first are the last to unite, while those which appear later, such as the epiphyses of the phalanges and metacarpal bones, unite first. Following this line of study, therefore, we find that the epiphyses of the distal phalanges unite first and then those of the metacarpals and of the other phalanges. These periods of unification correspond to the fifteenth up to about the seventeeth year and furnish us with a means of determining the individual's degree of development. It is during this period that one can determine whether a sufficient development has taken place to warrant the admission of a candidate to the Naval Academy.

Plates 1 and 2, taken by Professor Pryor, of Lexington, Kentucky, show the hands of two boys each seventeen years of age. Plate 1 shows the union which is to be expected at that age, while in Plate 2 the development is seen to be below the average in that none of the epiphyses have begun to ossify.

It might be well to mention here that Prof. Pryor also took Röntgen pictures of the elbows, ankles, and knees of these same boys and found that they corresponded to the development of the hands in each case.

Here, again, as in the earlier period of development, the question of chronologic age comes up, for at times the development of an individual of even fifteen years of age is found to be equal to that of a much later period.

Many more cases must, of course, be studied in this earlier part of the second half of development before a definite opinion can be given as to what degree of epiphyseal development a candidate for the Naval Academy should have before he is considered fitted to enter.

In this connection Plate 3 is certainly very significant in that it shows that at times certain individuals are fitted to enter at fifteen years, the age by law for entrance being sixteen years. This is the hand and wrist of a boy fifteen years of age. The union of the epiphyses represents a degree of development far beyond what is usually attained at that age and in fact one that corresponds to individuals three to five years older. This young man's mental development corresponded to his anatomic development and he certainly was well fitted to be at the Academy with older individuals. On the other hand, Plate 4 shows the hand of another boy, fifteen years of age, in which the development is far below the average, as shown by the undeveloped condition of the epiphyses.

Such cases as these impress upon our minds what we have so often insisted upon before in speaking of the grading of children in schools and in labor, that chronologic age cannot be depended upon for the determination of fitness for study or for occupation.

The work which has been done so far at the Academy by Dr. Smith has been carried on for the most part with older individuals, and for the determination of their epiphyseal development it has been necessary to make use of an epiphysis which, following the rule for early appearance and late union, was fitted for this purpose. This epiphysis is that of the radius, and it is the method which is being employed by Dr. Smith in grading these older individuals rather than the ultimate summing up of the results for the Government which we are presenting to you in this paper.

It must be understood that while we consider the epiphyseal development a very prominent and important factor in the problem of grading the cadets, that it is only a factor and not the complete representative of physical fitness for the training at Annapolis. It should be understood that comparative anthropometric charts, showing the entire physical development, are also used.

A great point to be considered is whether the factor of epiphy-

PLATE 3

Male, aged fifteen years.

PLATE 4

Male, aged fifteen years.

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seal development is in some way connected with the mental development, while the other factors are not. It should also be borne in mind that it is the equilibrium of mental and physical development which should be watched, this being accomplished by having Röntgen pictures taken from time to time as the cadet is advanced and to thus determine whether he should be advanced or even retained in the Government's service.

While what has just been explained can in a general way be used for determining the fitness for entrance and the advisability of advancing the individual from class to class, yet Dr. Smith is carrying out at Annapolis a much more detailed plan of studying the ossification of the epiphyses. A report of this work will appear later, but the general idea and scope of the work, so far as it has gone, is as follows: Each cadet's record is kept by means of his series number on a folder. The folder shows the name, age, weight, and strength group, the group classification being based on the exhaustive strength tests conducted by P. A. Surgeon W. N. McDonell, U. S. N. In this record, as shown in the sample folder, are also recorded remarks on any injuries, diseases, or other defects, Röntgen data, and the results of the Röntgen study of the epiphyses.

The next step is to refer each individual's epiphyseal development to the test of this general chart, Type Chart A, which will represent, after it has been made up from a large number of cases, the average epiphyseal development for the age of the individual and thus indicate whether as an individual he is advanced or retarded in such development.

This chart is one of four made for each epiphysis and represents the lower epiphysis of the radius half united. This Type Chart A is constructed with the abscissa representing the various ages, and coördinates the number of individuals of that age whose stage of development qualifies them for that chart. The lower epiphysis of the radius, for example, furnishes one series of charts, and in this series are four charts, one for cases in which union is begun, one for those in which union is one-quarter completed, one where it is one-half completed and nearly amalgamated, and one for those showing a distinct line or a slight notch; a fifth may be added for completed cases.

FOLDER.

Date

No.

Name Graduates

Age on date

Height Weight Group

Social status

Parentage

Home hygiene { city / country

Previous diseases and notes:

Actual age

Apparent age

Radiographic age

Tube, soft, hard

Amperage distance

Milliamperage

Internal Epitrochlear: Union

Line

External Epitrochlear: Union

Line

Olecranon: line,

Radius, head: Union,

Line

Ulna, lower: Union,

Line

Radius, lower: Union,

Line

Metacarpals: Union

Lines,—2

" 3

" 4

" 5

sessamoids

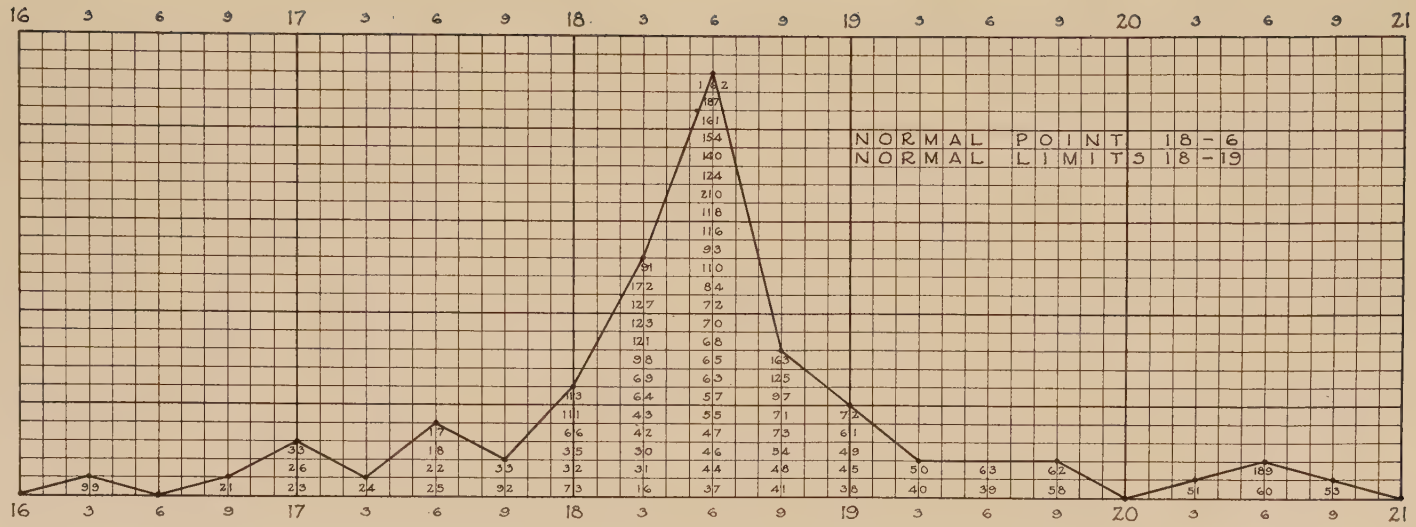
Phalanges: Union,

Lines,—2

" 3

" 4

" 5



TYPE CHART A.—Lower radius; half completed, 75 men.

The divisions are arbitrary and must necessarily be rough. For statistical purposes it is intended to increase the number of divisions to seven, but for practical use it is believed that four are sufficient.

The curves are formed in this way: All the plates in which the union of the lower radius is half completed, for instance, are collected together. Then under the age figures columns are built up by filling in squares with the series numbers of the plates. That is, John Smith's radius is in stage No. 2 and so is recorded on the chart, "Lower radius No. 2." His age is eighteen years, six months, and his series number is 161. Then we fill one square on Chart Radius No. 2 with "161" placed in the column under "18-6." The height attained by the column under "18-6" indicates, therefore, the absolute number of men of this age whose radii are in this stage. By connecting the tops of this and the other columns we construct a curve which represents graphically the age distribution of this stage of development. The highest point of the curve may be assumed to indicate the age at which the radius should be half united, thus establishing a normal age for that stage, or a normal stage for that age.

In order to standardize an individual, or find whether his chronologic and anatomic age correspond, a Röntgenogram is first taken. We shall assume that the lower radius is half united and that his age is 19-6. By reference to our curve we see that this stage of development should have been reached at 18-6, although the curve is still high at 18-9 and 19. Therefore we can see at a glance that his maturity is delayed by six months or a year, that he is 19-6 chronologically and but 18-6 anatomically, or that he is in Class "R" when he should be in Class "T"; "R" and "T" simply representing the especial anatomic index which we have referred to before as a final classification for grading.

The curve can be condensed to a table which will give data sufficient for comparison or standardization. The squares, instead of being blocked out, are filled with numbers, to facilitate reference to cases; except for studying this series of cases the numbers simply indicate an individual and a blocked square. The total number of cases entering into the formation of a curve may be easily read.

In this study there must be some allowance made for normal variations, and the limits of variations are obvious in the curves.

Each of the four curves, within its normal limits, has been transcribed on a reduced scale to one chart for purposes of ready comparison. This combined chart, *Type Chart C*, affords all the data necessary for age determination, but does not include the total number of cases entering into the curve or the extreme limits of departure.

For general information relative to these charts, there are added an age curve, Chart D, and a table, Chart E, of the average age, weight, height, and strength of the midshipmen arranged by classes. Chart D represents a chronologic curve. Later in the government report an epiphyseal curve will be represented on Chart D, the same chart, for comparison.

CHART E.—*Average Age, Strength, Height, and Weight for 1909–1910.*

Class.	No. of midshipmen.	Strength.	Weight.	Height.	Age.
1910	133	6346 lbs.	146.2	68.3	22–4
1911	201	6395 lbs.	146.1	68.2	21–3
1912	190	6397 lbs.	146.3	68.1	20–1
1913	191	6099 lbs.	144.1	68.2	19–4

Total number of midshipmen . .	715 (in age curve, 688 men.)
Average strength	6309
Average weight	145.6
Average height	68.2
Average age	20 years, 10½ months.

Having in this way established our norms or standards, an attempt will be made to estimate the practical value of anatomic age determination, although the rigid physical examinations in force act to hamper us by rapidly eliminating all defectives. The anatomic age of each student will be ascertained and the extent of his departure from normal noted with its direction—whether anticipatory or delayed. They will then be studied statistically to learn:

Per cent. of the whole student body delayed;
Per cent. of defective physiques delayed.
Per cent. of underweight delayed;
Per cent. of heart cases delayed.

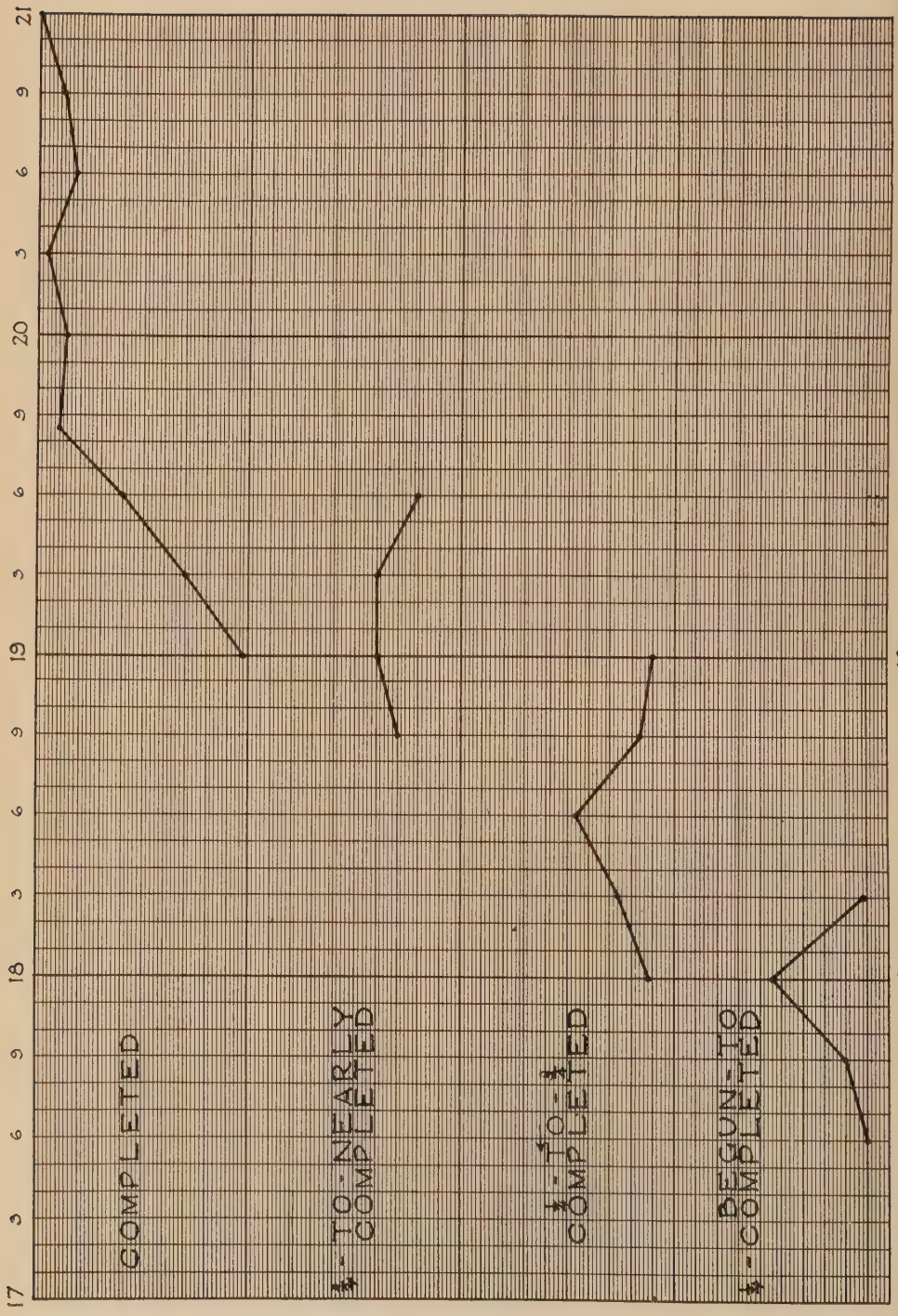


CHART C.—Lower radius, combined chart showing by curves the normal limits of variation in the four stages.

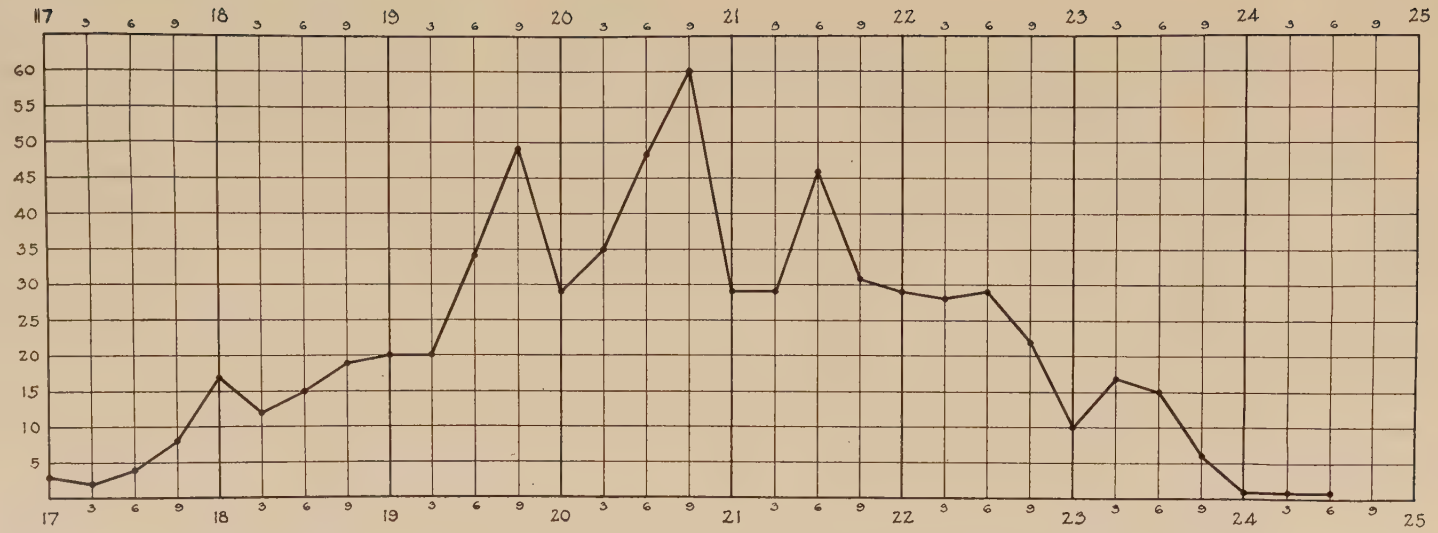


Chart D.—Chronologic age curve for whole student body, 669 men.

By this method we may gain some idea of the potency of relative immaturity in the production of defectives. In conjunction with Dr. McDonell there will be undertaken a study of the men in the crew to discover if there be any correspondence between immaturity and reserve vitality so far as it may be indicated by reactions of the vaso-motor system.

Anatomic points will not be neglected. The age at which epiphyseal union is begun and completed will be noted and likewise the method by which it is accomplished. Of particular interest is the manner in which ossification progresses. The cartilage is not invaded in an orderly and progressive manner, but on the contrary, discs of ossification appear independently, as in Plate 5. These are superposed and form imbrications in the clear cartilage. At a later stage these isolated discs or plates coalesce and produce irregular, multiple, branching lines, as in Plate 6. When fusion is complete there remains a thick line which grows fainter and shorter and finally disappears, as seen in Plate 7. Certain parts of an epiphyseal line show a more advanced stage than others, but in general amalgamation is complete in the centre while there is in the periphery a lack of calcification which appears on the plate as a notch. There are still other signs by which we can judge the recentness of a process which is completed. In the above charts the lower epiphysis of the radius has been selected as an example.

DISCUSSION.

Dr. George Dock: It would be interesting, if it has not already been done, to examine the same young men for hookworm. About one-fourth of the young men of the same age and social class in the South are hookworm carriers. Severe hookworm infection causes a very marked effect on bone development, so that in a patient whose skiagrams I was fortunate enough to get Dr. Rotch to examine, a young man, aged twenty-two years, who was generally taken to be a boy aged fourteen years, the Röntgenograms showed a bony development corresponding to about eleven and a half years. I have not been able to examine milder cases, but many hookworm carriers are very slow in finishing their growth; some of them grow after thirty years. Weight is very often less than normal for the height of the individuals, and retarded intellectual activity is sometimes possible to detect.

PLATE 5

Intracartilaginous disks of ossification in radius

PLATE 6

Coalescence of intracartilaginous disks producing irregular, branching lines.

PLATE 7

Fusion complete. Line of union in the process of disappearance.

Dr. Rotch: In answer to Dr. Dock's remarks about hookworm, I would state that I had been studying a certain number of these cases at the time when I spoke on this subject in connection with Dr. Stiles, at Columbia. Dr. Stiles explained how to get rid of the hookworm, and I showed how the epiphyseal development of the individual in his undeveloped picture, as shown by the Röntgen rays, could aid in deciding what should be done for him, and how he should be graded as to vocation. I also emphasized not only how the hookworm cases showed a delayed epiphyseal development, but how any disease or condition which interfered with metabolism might also cause such delay.

FURTHER STUDIES ON THE IMMUNIZING EFFECT OF MIXTURES OF DIPHTHERIA TOXIN AND ANTITOXIN.

By THEOBALD SMITH, M.D., and HERBERT R. BROWN, S.B.

(From the Antitoxin Laboratory of the State Board of Health of Massachusetts.)

In a former communication one[1] of us reported a series of experiments on guinea-pigs, designed to test the relative immunizing power of mixtures of diphtheria toxin and antitoxin. The results obtained showed that when mixtures are injected in which there is enough surplus toxin to produce local necrosis and ulceration of the skin, the active immunity which follows is relatively very high, whereas the injection of a single dose of toxin alone, which produces the same local reaction, does not lead to any appreciable immunity. When the amount of surplus toxin in the mixture is reduced, the resulting immunity is lower. When the mixture is just balanced or neutral, producing no local lesion, loss in weight, or subsequent paralysis, there is still active immunity produced. It was even possible to produce active immunity when the amount of toxin in the mixture fell below the neutral level. Contrary to expectation, immunity was still produced when such mixtures were allowed to stand several days at ordinary temperature.

To determine the degree of immunity produced, only female guinea-pigs were treated, and the passively acquired resistance of successive litters of their offspring tested at the uniform age of thirty days. This method made it possible to follow the immunity of the mother for a period of seven or more months, by testing successive litters, former experiments having shown that the active

[1] Journ. Exper. Med., 1909, xi, 241.

immunity of the treated female may last several years and remain during this time at a nearly constant level. The experiments upon which these statements are founded were made with great care. In order to eliminate even individual and family variability, female individuals of the same litter only were included in the same test. Lest there be any misunderstanding, it should be stated that we do not deny that even a single injection of toxin alone produces some active immunity, but it is probably very slight and does not show itself by any appreciable gain in the resistance of the offspring. How delicate our method may be as compared with the determination of the antitoxin content of the blood of the treated animal directly, we have as yet no accurate information. Among the facts which stand out in this first paper are: (1) The possibility of producing a relatively high degree of active immunity with mixtures of diphtheria toxin and antitoxin, which produce no immediate or remote, local or general effect upon the animal treated. (2) Standing for two to five days does not destroy the immunizing power of the mixture, but standing for two days seems to produce a higher resistance than standing only fifteen minutes or five days.

In the present paper these experiments are extended somewhat, and compared with other methods of immunization. The same methods were employed as heretofore, the passive immunity of the offspring being used as a measure of the active immunity of the treated female. All guinea-pigs used were normal in resistance—*i. e.*, not descended from treated guinea-pigs. In Table I are given all necessary data of an experiment designed to bring out what active immunity, if any, may be induced by injecting a mixture of toxin and antitoxin in which the toxin is reduced to somewhat less than one-half the dose contained in the neutral (Lo) mixture, or, what is the same thing, in which a double dose of antitoxin is added to the Lo dose of toxin. The Lo dose of the toxin used was between 0.15 c.c. and 0.17 c.c. In order to have a basis for comparison, a control pig of the same litter was treated with the neutral mixture, or Lo dose (0.15 c.c. + 1 unit). This experiment was duplicated at the time by treating two pigs belonging to another litter with similar mixtures, which were kept four days at ordinary temperature before injection. Two litters of each treated guinea-pig were tested.

TABLE I.

Mother.								Offspring.					
Litter.	Designation.	Dose injected in cubic centimeters.	Remarks.	Result.	Second dose injected in cubic centimeters. [Period between first and second dose.]	Result.	Period between treatment of mother and birth of litter.	Age in days.	Weight in grams.	Dose of toxin + one antitoxin unit in cubic centimeters.	Result.	Normal L + dose.	Estimated L + dose.
I	8259	0.15 toxin + 1 unit antitoxin.	Toxin-antitoxin mixture injected 15 minutes after preparation.	No lesion.	0.35 toxin + 1 unit antitoxin [8 months, 10 days].	Transient induration.	3 months, 8 days.	First Litter.					
								34	200	0.28	Large ulcer.	0.235	0.28+
								31	231	0.28	Small ulcer.	0.235	
								31	216	0.25	No lesion.	0.235	
							7 months, 19 days.[2]	Third Litter.					
								32	291	0.28	Large ulcer.	0.235	
								32	280	0.26	Moderate size ulcer.	0.235	0.28+
	8261	0.15 toxin + 2 units antitoxin.	Toxin-antitoxin mixture injected 15 minutes after preparation.	No lesion.	No test.	.....	3 months, 9 days.	First Litter.					
								38	220	0.235	Dies 3½ days.	0.235	0.235+
								30	192	0.25[1]	Dies 1½ days.	0.235	
							10 months, 25 days.[2]	Third Litter.					
								28	155	0.29[3]	Dies 2 days.	0.29[3]	
								28	170	0.29	Dies 2½ days.	0.29	0.29
J	8258	0.15 toxin + 1 unit antitoxin.	Toxin-antitoxin mixture injected after it had stood 4 days; 1 day at 70–75° F; 3 days at 62–65° F.	No lesion.	0.35 toxin + 1 unit antitoxin [8 months, 10 days].	Transient induration.	4 months, 4 days.	First Litter.					
								30	247	0.25	Transient induration.	0.235	0.25++
								30	266	0.235	Transient induration.	0.235	
							7 months, 21 days.	Second Litter.					
								30	221	0.28	Dies 7½ days.	0.235	
								30	201	0.26	Large ulcer.	0.235	0.29
	8257	0.15 toxin + 2 units antitoxin.	Toxin-antitoxin mixture injected after it had stood 4 days; 1 day at 70–75° F.; 3 days at 62–65° F.	No lesion.	0.35 toxin + 1 unit antitoxin [8 months, 10 days].	Slough, 2 inches in diameter.	4 months, 8 days.	First Litter.					
								30	258	0.25	Large local lesion.	0.235	
								30	252	0.30	Dies 2½ days +.	0.235	0.275
								30	255	0.275	Dies 3 days +.	0.235	
							7 months, 17 days.	Second Litter.					
								30	220	0.26	Dies 3 days.	0.235	
								30	217	0.24	Dies 3½ days.	0.235	0.25
								30	237	0.28	Dies 2½ days.	0.235	

[1] Part of mixture injected into peritoneal cavity.
[2] All of second litter died soon after birth.
[3] Another standardized test toxin whose L+ dose was at this time 0.29 c.c., was used in this test.

From the table it will be seen that the treatment preceded the beginning of pregnancy by about one month in one set and two months in the other. Subsequent pregnancies began from five to eight months after treatment. There was, therefore, no chance for directly influencing the fœtus in utero by the injection.

Taking the set treated with mixtures injected fifteen minutes after preparation, we see that the offspring of the pig receiving simply the neutral mixture showed considerable resistance, the estimated L + dose being 0.28 c.c., instead of 0.235 c.c. toxin. The offspring of the pig receiving the same amount of toxin, to which 2 instead of 1 antitoxic unit had been added, showed no increased resistance. In the second set, treated with mixtures four days old, the offspring of the female treated with the neutral mixture showed a resistance equivalent to $\frac{29}{235}$. The first offspring of the female treated with the same toxin, plus 2 antitoxin units, showed some resistance, the second, only a very little.

Turning to the treated females themselves, we note that in the final test made upon them over eight months later, the different early treatment is clearly reflected in the result. Unfortunately, only 3 of the 4 were tested. The dose injected should have proved fatal in all cases to a normal guinea-pig of the same weight.[1] It produced, however, only a transient induration in the two animals treated originally with the neutral mixture and a large area of local necrosis and ulceration in the one receiving the double amount of antitoxin.

Thus, even a mixture which contained a large surplus of antitoxin, and which had stood four days, produced still enough immunity to manifest itself in the treated animal and in the offspring.

It is not possible to draw the inference that the standing had slightly increased the immunizing power of the mixture, as might appear from the records, for the capacity to produce antibodies may have been greater in Litter I than in J. As already stated earlier tests pointed in the inference that standing for several days actually increased the immunizing power of the mixtures.

In Table II the immunizing action of neutral and slightly toxic

[1] See Table I of preceding paper for controls.

mixtures of toxin and antitoxin is tested by injecting subsequently small doses of toxin alone. Here a distinct gain in resistance is evident, since the test dose of toxin administered would ordinarily have produced necrosis and ulceration.

TABLE II.

No.	Weight.	Doses of toxin in cubic centimeters plus 1 unit antitoxin.	Result.[1]	Dose of toxin alone.	Days after first injection.	Result.
8577	266	0.18	Moderate transient œdema on third day.	0.002 c.c.	36	Slight induration and superficial scaling of skin.
8595	282	0.17	No lesion on third day.	0.002 c.c.	36	Slight induration and superficial scaling of skin.
8550	292	0.16	No lesion on third day.	0.002 c.c.	36	Large œdema with superficial scaling, but no ulceration.

It had been frequently observed that female guinea-pigs which had recovered from the effects of a very large or nearly fatal dose of toxin did not subsequently transmit any passive immunity to their offspring. It was therefore thought best, in order to compare the immunizing power of pure toxin as contrasted with toxin-antitoxin mixtures, to inject repeatedly doses of toxin alone over a long period. Owing to the great sensitiveness of the guinea-pig, only very minute doses of toxin can be injected, since doses less than one-tenth of the minimum fatal dose are still capable of producing local œdema, and in some cases necrosis.

As Table III shows, one animal was treated seven times; two, six times; and one, three times. The injections were made three to four weeks apart. This interval was required for the healing of the lesions produced by the preceding injection and to eliminate any cumulative action of the poison. The total amount of toxin which was injected in this way was very small, amounting to 0.0095 c.c., 0.0098 c.c., 0.0085 c.c., and 0.0023 c.c., respectively. The largest amount utilized during a period of four to five months was thus barely one and one-half times the minimum fatal dose. The degree

For controls see Table III for effect of small doses of toxin on untreated animals.

of immunity attained was tested on two litters of each pig. In three cases no immunity could be demonstrated. In the fourth, a distinct increase in resistance was produced. Why one out of three animals treated practically alike should acquire a relatively high degree of immunity is not explicable. Such exceptions, however, are met with among all species, and they must be accepted as variations.

Another series of experiments was next taken up, and the mode of administering toxin and antitoxin changed. A relatively large dose of antitoxin was injected subcutaneously, and then, twenty-four or forty-eight hours later, the toxin was injected, also subcutaneously and on the opposite side of the body. Table IV supplies all the necessary data. The amount of antitoxin injected was, in all cases but two, sufficient to protect the animal from any local effect of the toxin injected subsequently. From only one of these two exceptional cases were animals reared and tested.

There was a very slight increase in the resistance of the first litter of two out of three guinea-pigs immunized during pregnancy. All the others showed no increased resistance, although one might have looked for some immunity in the one in which a local lesion occurred (No. 8912).

To determine further the protecting effect of antitoxin injected before the toxin additional tests were made, which are summarized in Table V. A series of animals were treated with rising doses of toxin twenty-four hours after a level dose of antitoxin. Although these experiments have no direct bearing upon the subject of the communication, since the immunity of the treated animals was not tested later, they are of interest in several particulars.

TABLE III.

Mother.					Offspring.							
Designation.	Date.	Dose injected in cubic centimeters.	Result.	Length of treatment.	Period between last injection of mother and birth of litter.	Age in days.	Weight in grams.	Dose of toxin inoculated + 1 antitoxin unit.	Result.	Normal L+ dose.	Estimated L+ dose.	Remarks.
						First Litter.						
8352	Aug. 19, 1908.	0.002	Slough and ulcer.	4 mos., 21 days.	5 months.	30	196	0.29	Dies 3 days, 1½ hr.	0.29	0.29	No resistance.
						Second Litter.						
	Sept. 25, 1908.	0.0015	Induration; loss of hair.	.....	7 mos., 7 days.	31	228	0.30	Dies 2¾ days.	0.30	0.29	
	Oct. 22, 1908.	0.0015	Induration; superficial necrosis.									
	Nov. 21, 1908.	0.001875	Œdema; superficial necrosis.									
	Dec. 25, 1908.	0.00125	Œdema; superficial necrosis.									
	Jan. 9, 1909.	0.0014	Œdema; scaling of skin.									
	Total=	0.009525										
						First Litter.						
8354	Aug. 26, 1908.	0.00075	Induration; superficial slough.	4 mos., 14 days.	4 months.	30	246	0.29	Dies 2¾ days.	0.29	0.29	No resistance.
	Sept. 12, 1908.	0.0015	Induration; ulcer.	.....	.....	30	255	0.29	Dies 2½ days.	0.29	0.29	
						Second Litter.						
	Oct. 2, 1908.	0.0015	Induration.	.....	6 mos., 7 days.	28	163	0.30	Dies 3½ days.	0.30	0.30	No resistance.
	Nov. 3, 1908.	0.0014	Induration.	.....	.....	40	245	0.30	Dies 3⅛ days.	0.30	0.30	
	Nov. 25, 1908.	0.002	Induration; ulcer.									
	Dec. 15, 1908.	0.00125	Œdema; paralysis.									
	Jan. 9, 1909.	0.0014	Œdema; loss of hair.									
	Total=	0.0098										
						First Litter.						
8467	Oct. 22, 1908.	0.001	Local necrosis.	4 mos., 17 days.	3 mos., 24 days.	32	320	0.30	Slight thickening of skin.	0.30	0.40 ±	Marked resistance
						Second Litter.						
	Nov. 21, 1908.	0.00125	Local necrosis.	.....	6 months.	30	257	0.31	Transient soft œdema.	0.31	0.40 ±	Marked resistance
	Dec. 15, 1908.	0.00125	Œdema; loss of hair.									
	Jan. 9, 1909.	0.00105	Induration; scaling of skin.									
	Feb. 1, 1909.	0.002	Transient induration.									
	March 8, 1909.	0.002	Transient induration.									
	Total=	0.00855										
						First Litter.						
8590	Dec. 26, 1908.	0.000625	Induration; superficial necrosis.	2 mos., 13 days.	4 mos., 11 days.	28	270	0.30	Dies 3½ days.	0.30	0.30	No resistance.
	Feb. 1, 1909.	0.00071	Induration.									
	March 8, 1909.	0.001	Induration; scaling of skin.	.....	6 mos., 20 days.	30	327	0.31	Dies 2½ days.	0.31	0.30	No resistance.
	Total=	0.002335										

TABLE IV.

Mother.						Offspring.						
Designation.	Number of units of antitoxin injected.	Quantity of toxin injected in cubic centimeters.	Interval between injection of serum and toxin.	Result.	Period between treatment of mother and birth of litter.	Designation.	Age in days.	Weight in grams.	Dose toxin + antitoxin 1 unit in cubic centimeters.	Normal L+ dose of toxin used.	Estimated L+ dose for guinea pig.	Result.
						First Litter.						
8601	50	0.075	48 hours.	No lesion.	41 days.[1]	8220	25	253	0.28	0.28	0.30	Ulcer; paralysis; recovery.
						Second Litter.						
					3 months, 18 days.	8973	28	183	0.29	0.29	0.29	Dies 2½ days.
						8975	52	254	0.30	0.30	0.30	Dies 4¾ days.
						9154	27	248	0.31	0.31	0.31	Dies 3⅙ days.
						First Litter.						
8615	50	0.05	48 hours.	No lesion.	3 months, 28 days.	8991	31	173	0.29	0.29	0.29	Dies 4 days, 1 hr.
						8988	42	220	0.30	0.30	0.30	Dies 4 days, 20 hr.
						Second Litter.						
						9164	31	215	0.31	0.31	0.31	Dies 3 days (—).
						First Litter.						
8617	50	0.075	24 hours.	No lesion.	35 days.[1]	8821	30	302	0.28	0.28	0.30	Ulcer; recovery.
						Second Litter.						
					3 months, 16 days.	8966	30	225	0.29	0.29	0.29	Dies 2½ days.
						8967	30	288	0.30	0.30	0.30	Dies 3 days.
						First Litter.						
8635	50	0.05	24 hours.	Transient œdema (?)	31 days.[1]	8818	30	223	0.28	0.28	0.28	Dies 6 days.
						8819	34	216	0.32	0.28	0.28	Dies 2 days, 2 hr.
						Second Litter.						
					5 months, 8 days.	9041	30	315	0.30	0.30	0.30	Dies 4½ days.
						9042	30	320	0.30	0.30	0.30	Dies 5½ days.
8919	50	0.01	24 hours.	No lesion.	3 months, 13 days.	9262	26	232	0.31	0.31	0.31	Dies 2½ days.
8956	50	0.015	24 hours.	No lesion.	3 months, 17 days.	9268	28	175	0.31	0.31	0.31	Dies 2½ days.
8954	50	0.01	48 hours.	No lesion.	3 months, 18 days.	9257	27	238	0.31	0.31	0.31	Dies 3½ days.
8912	50	0.015	48 hours.	Small ulcer	3 months, 11 days.	9263	28	217	0.31	0.31	0.31	Dies 3½ days.
8934	50	0.01	72 hours.	No lesion.	3 months, 13 days.	9255	26	230	0.31	0.31	0 31	Dies 2⅔ days.
8935	50	0.15	72 hours.	Small ulcer		Offspring not used.						

[1] Immunization took place during pregnancy.

TABLE V.

Designation.	Number of units of antitoxin injected.	Quantity of antitoxin injected in cubic centimeters.	Interval between injection of serum and toxin.	Result.
8611	50	0.05	24 hours.	No lesion.
8602	50	0.10	24 hours.	Superficial slough, ½x⅛ in. diam.
8599	50	0.15	24 hours	Superficial slough, ½x¼ in. diam.
8625	50	0.20	24 hours.	Slough, 1x⅜ in. diam.
8627	50	0.25	24 hours.	Slight transient œdema.
8628	50	0.30	24 hours.	Slough, 1¾x1¼ in. diam.
8634	50	0.35	24 hours.	Slough, 1½x1½ in. diam.
8701	50	0.40	24 hours.	Slough, 1½x1½ in. diam.
8640	50	0.45	24 hours.	Large slough, 1½x1½ in. diam.
8643	100	0.10	24 hours.	No lesion.
8641	100	0.15	24 hours.	No lesion.
8653	100	0.20	24 hours.	Transient œdema.
8655	100	0.25	24 hours.	Slough, ½x½ in. diam.

It is obvious from the data given in Table V that 50 units of antitoxin, given twenty-four hours before a dose of toxin, so protected the animal that no local lesion followed a dose of 0.075 to 0.1 c.c. of toxin. Above 0.1 c.c. toxin a local lesion resulted. When the antitoxic dose was doubled, so that 100 units were given, the local lesion appeared at a dose of 0.25 c.c., or a trifle more than twice the dose needed when 50 units preceded.

When the dose of toxin was pushed beyond this point, the local lesion became gradually more severe, showing that the local immunity had been overcome. Although the ascending doses of toxin increased by seven times the minimum fatal dose at each step, yet the antitoxin stored in the body neutralized sufficiently the surplus toxin which escaped from the surcharged locality where it was deposited to protect the life of the animal. To what height the toxic dose could have been raised before the animal would have succumbed was not determined. The L + dose under these conditions is probably near 0.60 c.c. when 50 units antitoxin precede it by twenty-four hours. In this table individual variations among guinea-pigs is again brought out by No. 8627, in which the local lesion is less severe than in three others receiving from 20 to 40 per cent. less toxin.

The very much larger amount of toxin which the antitoxin can make harmless when the two are mixed before injection, than when the union occurs through the intervention of the body fluids, is once

more quantitatively represented by these tests. Experiments to determine whether any active immunity is generated when toxin precedes the antitoxin are now in progress.

Without going into any extended speculation concerning the mode of action of the toxin-antitoxin mixture, we wish to emphasize a few points of view which we have found difficult to disregard or overlook. If we assume that it requires an equal amount of energy to raise the body of the guinea-pig to the same immune level, whatever method of immunization is adopted, the resistance produced by toxin-antitoxin mixtures is probably due to a wide coöperation of different tissues no one of which is appreciably injured in the work, whereas, the attempt to produce immunity by injection of pure toxin forces certain tissues where the toxin is deposited to do nearly all the work. The locality is strained and even minute doses produce injury. In order that the immunization may be started by different tissues at the same time, it becomes necessary to get the toxin diffused. This diffusion we assume is effected by the toxin-antitoxin combination, which is not completely saturated with antitoxin. The avidity of the toxin is thereby so reduced that it is not held to any extent by the tissues where it is deposited, but it becomes diffused and only gradually bound. The antitoxin, as it were, smuggles the toxin into the body by disguising it. This procedure, which gives us an easier way to immunity, is likewise a source of danger, since it may bring the toxin to the nervous system and lead to paralysis.

It may be asked how we can explain the gradually rising immunity in animals, such as the horse, which is due to the local injection of pure toxin, for, according to the above hypothesis, such toxin would be held locally with greater and greater avidity as immunity progresses. This would be the result provided no free antitoxin were formed and the receptors remained sessile. But with the gradual production of increasing quantities of antitoxin, locally a larger and larger portion of the injected toxin is bound to the free antitoxin and carried to other territories which come under the influence of the combination until all the tissues capable of producing antitoxin are called into action. The body will have then reached its maximum productivity, beyond which it cannot go. All students

of immunity know that there is a limit set for each species, and in each species for individuals.

The tendency of injections of diphtheria toxin to produce a high local plus a lower general immunity in horses, is illustrated in the appearance of local necroses following the injection of toxin into new territories of the subcutis. When all the territories into which toxin is to be injected are gradually immunized together, abscesses do not, as a rule, occur. When, however, a new place is chosen, after a certain period of treatment and the usual dose injected, necroses may be expected. We have not observed any local abscesses for six or more years among the horses of this institution by obeying the rule here formulated.

This hypothesis, which makes use of the reduced avidity of toxin in unsaturated mixture with antitoxin in extending the territory producing immune bodies, is simply a slight modification and extension of present theories. Hypotheses being largely scaffolding for furnishing a foothold in the building up of facts, we place no special value on the one here presented, excepting in so far as it helps to stimulate further investigations tending to make the facts of practical use.[1]

[1] After the above article had been completed our attention was called to a preliminary paper by William H. Park on a similar subject (New York Pathol. Soc., May, 1903.) In his experiment one group of horses received toxin to which was added six times the amount of antitoxin necessary to neutralize it for the guinea-pig. Another group received toxin containing one and one-half times the necessary neutralizing dose. In the former very little antitoxin was produced, in the latter relatively large amounts were produced quite rapidly.

ROYAL SOCIETY
20 MAR
1911

THE BACTERIOLOGY OF ACUTE RESPIRATORY INFECTIONS IN CHILDREN AS DETERMINED BY CULTURES FROM THE BRONCHIAL SECRETION.

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In December, 1908, an investigation was begun in the Babies' Hospital to determine what information could be gained in respiratory infections from a study of cultures of bronchial secretions. For the first season interest centred upon the B. influenzæ, to gain, if possible, some definite information as to its frequency and importance in respiratory infections, and also to see what value, if any, could be attached to sputum cultures in the diagnosis of influenza. The first season's observations extended from December, 1908, to June, 1909, and were made upon 250 patients and 40 nurses in the Babies' Hospital. The methods pursued and results obtained have been set forth in a previous paper.[1] They indicated that the B. influenzæ played a very important part in respiratory infections, especially in winter and early spring, being second in importance only to the pneumococcus. Our observations, however, showed that it played no part in these infections during the warm months, for it disappeared entirely toward the end of May, as soon as permanent warm weather came, and it was not found again until about the middle of October. Pneumococcus infections, on the contrary, persisted throughout the summer months.

During the past season the scope of the study has been somewhat

[1] Archives of Internal Medicine, May 15, 1910.

enlarged and has included observations on the occurrence in the secretions of the respiratory tract, both of healthy and diseased persons, of the pneumococcus, the B. influenzæ, the Staphylococcus aureus, and the streptococcus. In our present report we are not especially concerned with the diphtheria bacillus, and it will be mentioned only casually, although it was noted when present. Nor has there been included in the tables of this paper a detailed report concerning the Micrococcus catarrhalis, which was found in about two-thirds of the cultures made. Thus far we have not been inclined to consider its presence as significant or important.

During the past season, from the middle of September, 1909, to June 1, 1910, there have been made from over 500 patients and 30 nurses and attendants over 1100 cultures from the secretions of the respiratory tract during life. There have been made, in addition, cultures from the lungs and heart's blood in 85 routine autopsies. It has been our custom to take a sputum culture from every patient admitted to the wards; at intervals to take cultures from all the inmates of the hospital—patients, physicians, and nurses. In most of the acute respiratory cases (especially in the protracted ones) repeated cultures have been made. Frequent cultures have also been made in most of the febrile cases of obscure diagnosis.

The patients were inmates of the Babies' Hospital, and for the most part under three years of age. In taking cultures, so far as possible, the bronchial secretion was secured. Control cultures were taken from the nasopharynx, pharynx, and nose in about 45 cases, to determine the variations. Anterior nasal and pharyngeal cultures often disagreed with the bronchial cultures, and hence were deemed rather unreliable as representing the nature of the respiratory infection. Results obtained from the nasopharyngeal cultures in the main corresponded closely with the bronchial cultures, but were much more difficult to obtain. To avoid contamination, it was found necessary, if there was much mucus present, first to cleanse the mouth and sometimes even the pharynx. A curved swab was then passed behind the soft palate into the nasopharynx.

The method of taking the bronchial cultures I have already described. It consists in inducing a hard cough by pharyngeal irritation, and catching upon a swab the secretion excited by the cough.

The cultures may therefore be considered to represent fairly accurately the bronchial flora rather than the pharyngeal flora.

The results of the clinical cultures made from September 20, 1909, to May 31, 1910, are shown in Table I. The patients are divided into four groups:

1. Those with pneumonia. Most of the pneumonias were of the acute primary type, bronchopneumonia being much more common than the lobar variety. Only a few of the pneumonias were secondary to other infections. A small number were terminal infections in children suffering from marasmus.

2. Those with bronchitis and other mild respiratory infections, laryngitis, tracheitis, etc. The cases included in this group were for the most part rather mild infections.

3. Those with pulmonary tuberculosis.

4. Those with non-respiratory diseases. These were surgical patients, children admitted for disordered nutrition (feeding cases) or other chronic disease, or healthy infants. In this group are included 30 nurses and attendants.

What a mixed infection the acute pneumonia of early life is this table shows in a striking manner.

Pure cultures were practically never seen, although a single dominant type of infection was present in very many cases. The table shows, in the different groups, the frequency with which the different organisms were found in the cultures, and also the number of patients in which they occurred.

In the first group, the pneumonias, and, in fact, in all the groups, the predominance of the pneumococcus and Staphylococcus aureus will be noted. The percentage of cases showing the B. influenzæ falls considerably below that observed in the previous season. The streptococcus was rarely the predominant organism found, although present, but usually in small numbers, in over one-half the patients and about one-third the cultures taken. The probable explanation of this small percentage is that few of the pneumonias were secondary to such infections as measles, diphtheria, etc.

TABLE I.—*Life Cultures (Bronchial), September 20, 1909, to June 1, 1910.* *Paracentesis Cultures.*

	Pneumonia.		Bronchitis, etc.		Pulmonary tuberculosis		Non-respiratory.		Acute otitis.	
	124 patients. 333 cultures.		133 patients. 364 cultures.		23 patients. 44 cultures.		254 persons (30 nurses). 374 cultures.		57 patients. 86 ears.	
	Patients.	Cultures.	Patients.	Cultures.	Patients.	Cultures.	Patients.	Cultures.	Patients.	Cultures.
Bacillus influenzæ . .	47	93	63	137	6	8	49	77	4	6
Pneumococcus	94	200	105	231	16	26	133	185	13	15
Streptococcus	63	120	71	109	12	16	130	153	15	17
Staphylococcus aureus .	116	257	117	266	16	34	216	300	44	57

Total, 1115 cultures; 534 persons (30 nurses). [B. diphtheriæ = 3.]

That the character of the infection in bronchitis is essentially the same as that in pneumonia is not generally appreciated. Thus in the second group of mild respiratory infections it will be noted that the relative frequency of the different organisms found in cultures is about the same as in the first group, except that the percentage of influenza cases is higher. In the third group, the tuberculous cases, the pneumococcus and Staphylococcus aureus still predominate.

In the fourth group, non-respiratory cases, it is not surprising to find the Staphylococcus aureus in about 85 per cent. of the patients, and of the cultures and the streptococcus in about one-half this number. It is, however, rather surprising to find that 52 per cent. of the patients showed the pneumococcus; but it should be remembered that the season was the winter and spring and the patients were hospital inmates. The proportion of influenza cases falls the lowest in this of any of the four clinical groups; but it was found in 19 per cent. of the patients.

I have appended to the table the results of cultures made from 57 cases of acute otitis after fresh paracentesis, as otitis is so frequently associated with acute infections of the respiratory tract in children. It is noteworthy that, while about one-half the patients with otitis showed the B. influenzæ in throat cultures, in only four patients (both ears in two of them) did the cultures made after paracentesis show the B. influenzæ; the predominant organism was the Staphylococcus aureus.

It is desirable, and we had hoped it might be possible, to connect certain clinical symptoms and definite cultural findings. In many cases with experience we were able to predict the predominant type of infection, but in very many others it was impossible. The great difficulty apparently lies in the mixed character of the infection, which has already been emphasized, so that the clinical picture, like the cultural findings, was usually of a mixed type. In one group, for instance, a predominant influenza infection; in another, a predominant pneumococcus infection; and in others, a predominant staphylococcus infection; but these were seen in all possible combinations. There were many variations in the clinical course of the infections which could not be explained by the cultures. In

fact, it became evident that a very extended experience will be required before this can be done with even an approach to accuracy.

Very few examples are seen of what we are accustomed to regard clinically as acute pneumococcus infection of the lung, viz., cases with an abrupt rise in the temperature, followed by a steadily high range and a critical fall. The pneumonia cases were for the most part atypical both in course and duration. It is my own belief that it is the other organisms present, especially the Staphylococcus aureus and the B. influenzæ, which are largely responsible for these variations.

In our own series of cases we were unable to see any definite modification of the symptoms in those which showed the streptococcus in the cultures, except in a few which were of exceptional severity.

The B. influenzæ was often present in small numbers when it did not appear to have any effect upon the symptoms, but many of the most irregular and puzzling cases were found to be associated with its presence. A study of this organism in quite a large series of cases led to the conclusion that when present in numbers it did produce quite definite symptoms. We came to recognize several fairly distinct clinical types associated with influenza infection:

1. Cases of pneumonia, often small in extent, sometimes with signs only of bronchitis, but with very wide and irregular fluctuations of temperature, which occurred without any apparent cause.

2. Very protracted cases with exacerbations and remissions.

3. Recurring cases of pneumonia in which a succession of attacks followed each other, separated by an interval of days or weeks, with partial or apparently complete recovery.

4. Cases showing constitutional symptoms of only a mild infection, judging by the pulse, the nervous symptoms, and the amount of general prostration, but with quite extraordinary fluctuations of temperature, which was usually high and very irregular in its course. A small area of pneumonic consolidation sometimes appeared late in these cases. However, there were in many instances no evidences of consolidation and only rales in the chest; these rales in some cases were few and inconstant.

The presence of the B. influenzæ was more frequently associated

with symptoms of the lower than with those of the upper respiratory tract. In general, influenza infections were characterized by mild general symptoms, by very irregular physical signs, and by wide and irregular fluctuations of temperature.

In the following case reports examples are given of what we have been accustomed to call influenza infections, together with the evidence upon which the diagnosis of influenza rested. The charts have been selected from a great number, and are fairly characteristic of the clinical conditions met with.

CASE I.—*Influenza; Bronchitis; Double Otitis; Later, Bronchopneumonia; Death; Autopsy.* The patient was a delicate child, aged nine and one-half months, admitted December 3, with a second attack of acute bronchitis; previously ill for one week. The entire family at home were reported suffering from coughs and colds at the time. On examination there were found moderate prostration and scattered rales throughout the chest. Three days later, on December 6, double otitis developed, and paracentesis was done on both ears. The operation was repeated on both ears on December 13, and again on the left ear on December 15 and 27.

The rales in the chest persisted, but not until December 21 were there any signs of consolidation of the lung, and then only over a small area. These signs never cleared up; the prostration steadily increased, and with failing nutrition the child died on January 16 of exhaustion.

During the course of the illness the principal interest attached to the wide fluctuations of temperature, chiefly between December 10 and 20. The daily excursion was at times as much as 10° F. There were no chills. Such a temperature occurring in a case of otitis after both ears had been opened, and with a constant tendency to close, led the surgeon to suspect sinus thrombosis or mastoiditis. Further operation was opposed, partly on account of the child's poor general condition, but also for the reason that, as the throat cultures showed the B. influenzæ, it was thought that this might be the explanation of the unusual temperature variations.

At autopsy a very small amount of bronchopneumonia was found. The cultures from the lung showed the B. influenzæ and the pneumo-

coccus. The mastoid and the sinus were carefully examined by the aural surgeon himself, and no trace of disease could be discovered.

CASE II.—*Influenza; Slight Bronchitis.* This child was under observation for three and one-half months, and in spite of the recurring attacks of temperature, he was never very sick, and gained steadily in weight, on the average about a pound a month. He was a delicate infant, aged nine months, weighing on admission but ten pounds. He was brought to the hospital on account of poor nutrition and a slight cough. A few coarse scattered rales in the chest could be heard most of the time during his stay, but there were no fine rales, and no signs of consolidation were ever present.

During the first period of fever, from October 13 to 23, the digestion was not particularly disturbed, and the pulmonary signs did not increase. No cultures were taken at this time. There followed then an interval of nearly two weeks, with normal temperature and no signs of illness except an occasional slight cough.

The second rise of temperature came on without apparent cause, with no obvious disturbance of digestion, and no new signs in the chest. No sufficient explanation of this temperature could be found and, as during the previous attack, he did not seem very sick, even when the temperature was as high as 105°. The urine was normal, and also the ears, though frequently examined. No malarial organisms could be found in the blood. The Widal test was negative, and the spleen was normal. The tuberculin test was negative. The leukocyte count was low, the average of several examinations being 7000; the polymorphonuclear percentage ranged from 31 to 36.6. Influenza was suspected, but repeated cultures from the bronchial secretion at this time failed to reveal this organism. The temperature subsided before any satisfactory diagnosis could be made.

After a normal interval of about a week a third period of temperature began, which continued nearly three weeks; although it was not quite so high as the previous attack, it was of the same irregular type. During this febrile period the sputum cultures showed the B. influenzæ constantly. There were no more general or local symptoms of illness than during the previous periods of fever. A positive agglutination reaction was obtained with the patient's own

influenza organisms. It is my belief that all the febrile attacks were due to the influenza, and that the organisms were missed in the early cultures.

Four injections, 75,000,000 each, of a polyvalent, heterogenous influenza vaccine were given to this patient on January 7, 13, 20, and 26. The temperature did not rise again, and the subsequent course suggests that some benefit resulted from the vaccines, but this cannot be definitely affirmed. As in the previous case, a disposition of the temperature to go to subnormal after the marked fall is noteworthy.

Case III.—*Influenza; Bronchopneumonia; Otitis; Death; Autopsy.* The patient was a delicate child, aged seven months, admitted, December 5, on account of its poor nutrition and cough. No symptoms of acute illness were present. During the first two weeks a slight rise of temperature was noted occasionally, as shown in the chart. The temperature was then normal until December 31. With this acute rise in the fever the symptoms of bronchopneumonia developed, with a small consolidation in the right lung. There was very little change in the signs or the symptoms for the next ten days. Otitis then developed, and both ears were opened on January 12. Three days after this a small spot of pneumonia was discovered in the opposite lung. The signs in the lungs did not increase with the high temperature, nor did they diminish with the fall in the temperature which succeeded. However, the child steadily lost strength and died from exhaustion.

The autopsy showed an ordinary bronchopneumonia of moderate extent; no other lesions of importance. The bronchial cultures during life repeatedly showed the B. influenzæ. Cultures from the lungs at autopsy showed the B. influenzæ, but no pneumococci.

Case IV.—*Unresolved Pneumonia; Influenza.* The patient was a boy, aged two years, admitted January 21, with a history of two months' illness, with pulmonary symptoms and a diagnosis of pneumonia. Temperature on admission was 103°. Physical signs pointed to a partial consolidation in right upper lobe behind. Leukocytosis, of 40,000; polymorphonuclear percentage, 79. By January 31 nearly all the signs in the chest had disappeared; leukocytosis, of 14,000. The patient continued to improve until February 7, there

being present in the chest during this time only occasional coarse rales, bronchovesicular respiration, and slight dulness over the area previously noted. Following the rise of temperature on February 7, an increase in the signs in the chest took place. More rales were present; they were of finer quality and over a larger area, but only on the right side. There was no definite consolidation. The leukocyte count ranged from 20,000 to 28,000 during the next few days. This exacerbation was but of brief duration, and after four or five days the only signs in the chest were those which had been noted before the rise in the temperature. During the following three weeks the irregular fluctuations in temperature shown in the chart occurred, with no special change in the local or general symptoms. The child coughed moderately, but did not appear very sick at any time.

Repeated sputum cultures showed the B. influenzæ. There was no temperature after that last recorded. Careful and repeated examinations were made, in this case, of the urine, the ears, and the blood, without revealing any other cause for the temperature. The inference seemed a fair one that the temperature was due to the influenza infection.

I think the cultures which we have made go far toward establishing the fact that the B. influenzæ plays a considerable role in the respiratory infections of young children. We have tried the use of influenza vaccines in about one-half dozen cases without any very decisive results, but I feel that this is a subject demanding further investigation. Their use is indicated especially in the very protracted or in recurring cases of influenza infection. Such an infection, we have shown, may continue for three months, and may probably last a much longer period.

With reference to the precise influence of the streptococcus and Staphylococcus aureus upon the symptoms and course of respiratory infections, I feel more hesitancy in expressing an opinion. The Staphylococcus aureus, I am convinced, plays a more important part in the bronchopneumonia and other respiratory infections of young children than has usually been accorded to it. We began our investigations with the view, which I believe is commonly held, that its presence was to be expected, not only in the sputum but in

autopsy cultures from the lungs, and th
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the symptoms of pneumococcus infection
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The following case, however, seems wo
strong impression upon all who followed it

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omitted was exactly like that which pre
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opened; subsequently the right ear was a
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The culture card of this patient for
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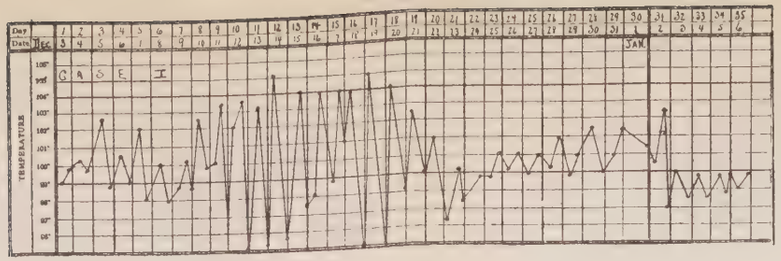

CHART 1.—Case I.

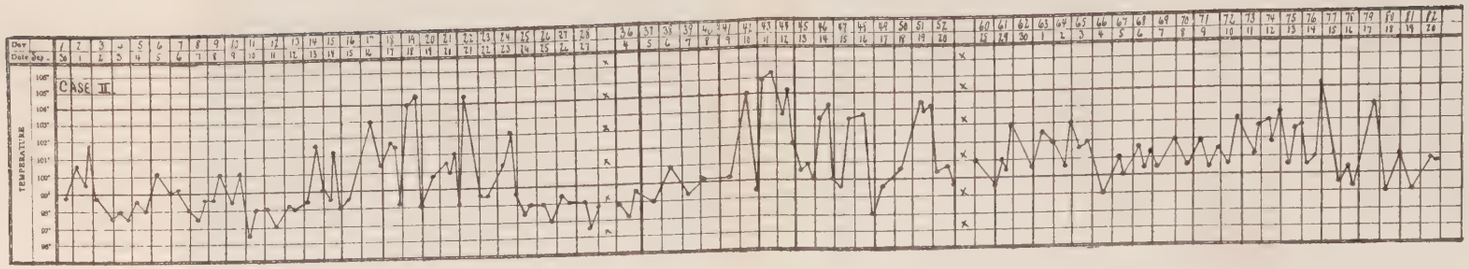

CHART 2.—Case II.

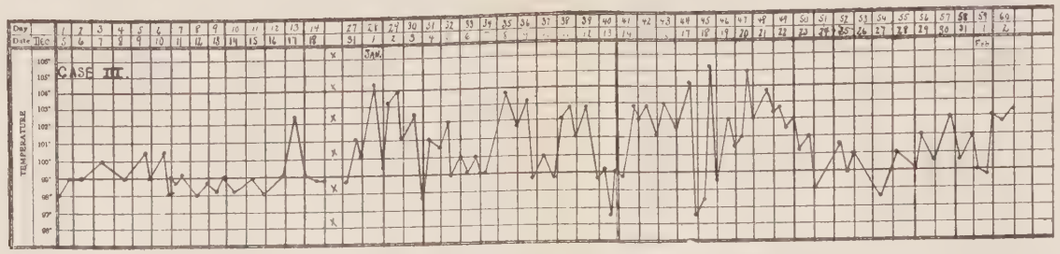

CHART 3.—Case III.

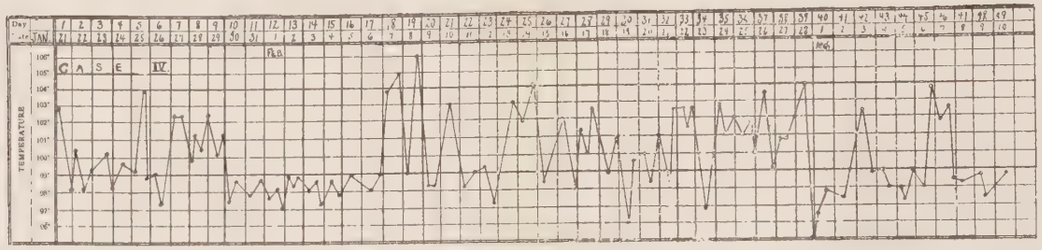

CHART 4.—Case IV.

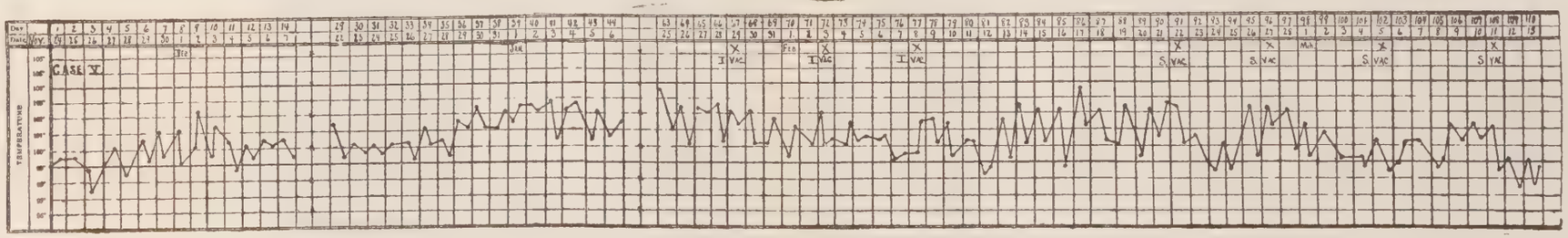

CHART 5.—Case V.

autopsy cultures from the lungs, and that it was not significant. But a wider experience has led us to modify this opinion. When present in numbers, the staphylococcus, I believe, distinctly modified the symptoms of pneumococcus infections. In some cases it certainly seems to be the predominant organism. We have found this to be true of some cases characterized by temperature not very high, and with rather narrow fluctuations and with constitutional symptoms of only moderate severity.

The following case, however, seems worth recording. It made a strong impression upon all who followed it.

Case V.—*Bronchopneumonia; Otitis; Cured (?) by Staphylococcus Vaccines.* This patient was a premature infant, aged seven weeks, and its weight November 25, when the temperature began, was only 3 pounds 12 ounces. The temperature continued in this case for more than three and one-half months. The complete chart is too long for reproduction, but the temperature for the periods omitted was exactly like that which preceded and followed them. The daily fluctuations were for the most part narrow, the usual range being 100° to 102.5°; it never touched 104°, and very rarely went to the normal line. During the greater part of this time there were localized coarse and fine rales in the right lung behind. These signs persisted and from time to time were heard throughout both lungs. There were no signs of consolidation at any time. The infant had a moderate cough, but never seemed very sick. The persistent physical signs and the temperature led to a suspicion of tuberculosis, but the skin test was negative and no tubercle bacilli could be found in the sputum. The blood showed a leukocytosis of from 12,000 to 16,000. The child's weight slowly increased to 5 pounds 14 ounces by March 13. On January 12 otitis developed and the left ear was opened; subsequently the right ear was affected, and opened January 20.

The culture card of this patient for January and February is reproduced in full, and shows exactly the findings on the different days. As influenza vaccines were being used at this time in some other cases, and as the influenza bacillus was at times present in the cultures of this patient, they were first tried. Three injections of a heterogenous influenza vaccine were administered on January 29,

February 3, and 8; the first dose was 50,000,000; the second and third, 30,000,000 each. Although the temperature was not quite so regular in its course during and for a few days after these injections, no real benefit seemed to follow.

CULTURE CARD OF CASE V.

Date.	B. influenza.	Pneumococcus.	Streptococcus.	Staphylococcus aureus	Source of culture.
January 6	—	+	—	+	Bronchial.
January 8	—	+	—	+	Bronchial.
January 20	—	—	—	+	Right ear.
January 26	—	—	+	++	Bronchial.
January 27	++	—	—	++	Bronchial.
January 28	—	+	—	++	Nasopharyngeal.
January 28	+	+	—	++	Bronchial.
February 9	—	—	—	++	Pharyngeal.
February 16	—	—	+	+	Bronchial.
February 20	—	+	+	++	Bronchial.
February 28	—	—	—	+	Bronchial.

During February several quite large furuncles appeared over the chest and abdomen. This circumstance, coupled with the persistence of great numbers of staphylococci in the sputum cultures, led to the suspicion that the essential process in this patient might possibly be a staphylococcus infection. On February 22, 27, and March 5 and 11, injections were given of a staphylococcus vaccine from a stock culture, the dose being 30,000,000 each time. The effect upon the temperature was immediate and striking, as is shown by the chart. After each injection there was a fall, and after the last injection no further rise occurred; but what was quite as surprising, the long persisting signs in the chest quickly and permanently disappeared. From this time the gain in weight rapidly increased, and the child was discharged quite well on April 25.

One hesitates to make any deductions from a single case, but the length of observation of this patient and the close study which was possible makes it worthy of the record. I cannot believe that cases of this kind are so very rare.

Postmortem Observations. Turning now to the postmortem findings, we have observations upon 138 autopsies made during the fall, winter, and spring months. I have included those of the season of

1908–1909 not previously published in detail. These autopsies were practically consecutive; cultures were invariably made unless the examination was hurried or partial. As a rule, autopsies were made early, most of them within twelve hours, and very many within six hours, after death. All bodies were immediately placed on ice, unless the weather was cold. Postmortem changes do not, I believe, play an important part in the findings. Cultures were made from the part of the lung showing the most extensive disease, and in every instance from both lungs. There was substantial agreement of the findings from the two lungs, so that it has not been thought important to separate them. The main facts are given in Tables II and III.

TABLE II.—*Postmortem Cultures (Routine Autopsies, Autumn, Winter, and Spring of 1908–09 and 1909–10).*

	Lungs, 138 cases. Pneumonia, 76; bronchitis, 20; tuberculosis, 29; non-respiratory, 13.		Heart's blood, 117 cases. (No growth in 71.)	
Bacillus influenzæ	37 cases	alone 4	1 case	alone 0
Pneumococcus	53 cases	alone 6	8 cases	alone 5
Streptococcus	43 cases	alone 1	22 cases	alone 17
Staphylococcus aureus	86 cases	alone 26	17 cases	alone 14
B. Diphtheriæ	12 cases	alone 2	2 cases	alone 1
Catarrhalis	7 cases	alone 0	0 cases	alone 0
Pyocyaneus	3 cases	alone 0	3 cases	alone 2
Bacillus coli	1 case	alone 0	2 cases	alone 1

TABLE III.—*Postmortem Cultures (138 Cases).*

Growth from lungs.	Pneumonia, 76 cases.	Bronchitis, 20 cases.	Pulmonary tuberculosis, 29 cases.	Non-respiratory, 13 cases.	Total.
Bacillus influenzæ alone	2	2	0	0	4
Pneumococcus alone	4	1	0	1	6
Streptococcus alone	1	0	0	0	1
Staphylococcus aureus	8	6	8	4	26
B. influenzæ and pneumococcus	5	1	0	0	6
B. influenzæ and streptococcus	5	0	2	0	7
B. influenzæ and staphylococcus	7	1	2	0	10
Pneumococcus and streptococcus	1	0	1	0	2
Pneumococcus and staphylococcus	11	1	5	2	19
Pneumococcus and catarrhalis	5	0	0	0	5
Staphylococcus and streptococcus	10	1	7	3	21

The remaining 31 autopsies showed various other combinations of the above organisms, or of them with pyocyaneus, B. diphtheriæ, or B. coli, but not more than two cases of any one variety.

It will be noted that of the 138 cases, there were 76 of pneumonia, 20 of bronchitis, 29 of tuberculosis, and in only 13 was there no disease of the lungs. The small number with no pulmonary disease is accounted for by the fact that no summer autopsies are included.

In general, the postmortem findings corresponded with the clinical findings by sputum cultures as indicating the type of infection. Mixed infections were seen in the great majority of the cases. The B. influenzæ was found in the lungs four times in pure culture; the pneumococcus was found pure in 6 cases. In this connection I should like to mention one case in which at autopsy a pure culture of influenza was obtained from a serofibrinous pleural exudate, and another in which a pure growth of this organism was obtained from empyema pus drawn by aspiration in a patient who recovered. This patient's bronchial secretion gave also a positive influenza culture.

Omitting the staphylococcus, a single organism was found in but 13 of the 138 cases. The significance of the finding of the staphylococcus alone in 26 cases is somewhat doubtful.

Cultures from the heart's blood were made in 117 cases, in 71 of which there was no growth. The B. influenzæ was found but once, and then not alone; the pneumococcus in but 8 cases, in 5 of these alone. Only the streptococcus and staphylococcus were at all frequent, being found, respectively, in 22 and in 17 cases.

Cultures such as those which we have been making involve considerable labor. Are they of any practical value to the physician? My own belief, after an experience extending over two years, is that they are of great assistance in diagnosis, especially in influenza infections. In cases where the symptoms led us, from our experience, to suspect influenza, we seldom failed to find the organism, usually in the first or second cultures, but occasionally not until repcated cultures had been made. These give much more definite results than the search for tubercle bacilli in suspected cases.

The discovery of the B. influenzæ in sputum cultures in cases of obscure high temperature, in cases of recurring bronchopneumonia, of pneumonia running an unusual course, or of high temperature persisting in cases of otitis in which the ears had been opened or after surgical operations, of course, does not establish the fact that

the temperature is due to this infection; but when this organism is found repeatedly and in large numbers associated with such symptoms, it is, in the winter and spring season at least, extremely probable.[1]

Further evidence that the presence of the B. influenzæ in the nasopharyngeal and bronchial secretion is significant, is shown by the fact that of three recent cases of influenza meningitis which I have seen, the cultures showed in each case the influenza organism in the nasopharynx, and in two in which the examination was made they were also present in the bronchial secretion.

No one realizes more than I that a much more extended study and many series of observations must be made before it will be possible to establish relationships between bronchial or nasopharyngeal cultures and clinical symptoms in respiratory infections. The separation of the respiratory infections is admittedly difficult, but I believe it to be quite as desirable as in the case of intestinal infections. To what extent vaccines may be found useful, it is impossible to say, but it is certain that any form of specific treatment must be based upon a knowledge of the nature of the infection.

In conclusion, I desire to express my indebtedness to Dr. Martha Wollstein, pathologist of the Babies' Hospital, and to Dr. Josephine Hemenway, resident physician, for their invaluable assistance in the observations recorded in this paper.

[1] Reference has already been made to the fact that in the Spring of 1909 our influenza infections disappeared after about May 20. Precisely the same thing happened this year. Thus, of forty-eight cultures taken between May 1 and 19, influenza was found in nineteen; of nineteen cultures taken between May 19 and 31, influenza was found but once, on May 23. At autopsy the B. influenza was found in cultures from the lungs but once after May 19, this being in a patient who was admitted two weeks previously.

DISCUSSION.

Dr. Frederick T. Lord: I have been much interested in Dr. Holt's paper—interested the more because his results differ in certain respects from those which I obtained from 1902 to 1905 in a similar investigation, dealing not with children, but with adults.

One hundred and eighty-six cases were studied, comprising for the most part infections classed clinically as bronchitis. The series was divided into groups according to the bacterial contents of the sputum. In about two-thirds there was a mixed infection. In the remaining one-third a single organism predominated.

An attempt was made to correlate the clinical picture with the bacteriological findings in the small group of practically pure infections, and most of these cases were followed to their termination. Infection with the influenza bacillus comprised the largest number. In a smaller proportion, the pneumococcus, micrococcus catarrhalis or other organism was an apparent cause. A study of the clinical features in the various groups led me to a different conclusion from that expressed by Dr. Holt. In the symptoms of onset, the course and duration of the different pure infections there seemed to be nothing distinctive. It was also found, as the case progressed, that the pure infections tended rapidly to become mixed, thus leaving me in doubt as to the relative importance of any one of the infecting agents.

In a study of the postmortem findings in 85 cases of bronchopneumonia, associated with various bacteria, I likewise failed to note any striking or constant difference in the character, extent, or intensity of the pathological process, either in the mixed infections or in those in which one organism predominated.

In regard to the leukocyte count in cases classed clinically as influenza, it seemed to me, from a review of about 230 such cases at the Massachusetts General Hospital, that in general the count varied according to the site of the infection, being usually unelevated when the upper parts of the respiratory tract were involved, commonly above normal with bronchitis and quite constantly high with pneumonia.

Dr. William S. Thayer: What Dr. Holt has said with regard to the occurrence of intermittent fever in influenza is especially interesting. My experience has been with adults, but I have been particularly struck by the manner in which the chart of a patient with influenza may simulate that of malarial fever. I have the records of two such cases. In one of these there were two sharp febrile paroxysms coming on exactly forty-eight hours apart, so that one looking at the temperature chart would surely regard the case as one of malaria, After the second paroxysm, however, there was an interval of three days. In another instance there was a remarkable picture of a paroxysm occurring at the same hour on successive days, closely simulating malarial fever. B. influenzæ was

obtained from each of these cases. It is encouraging to hear the reports of instances of meningitis with influenza, with recovery. I have seen two such instances, each was very virulent and fatal. The first case was reported by Dr. Samuel S. Adams, of this city.

Dr. W. H. Park: Dr. Holt emphasized two points: First, the importance of employing cultural methods, and secondly, the bearing this has on both the diagnosis and prognosis. We all agree that the most careful work is required in obtaining the material and in its examination before we should presume to give vaccines.

As to the value of cultural methods in diagnosis and prognosis, my experience has been more in the line with Dr. Lord.

One point not brought out was in regard to tuberculosis. Wherever, as at the Babies' Hospital, bacterial tests are carried out, it is shown that many cases supposed by the physicians to be cases of bronchitis or bronchopneumonia, or cerebrospinal meningitis, are really found to be instances of generalized tuberculosis. The majority of tuberculous cases in infants in New York City are not diagnosed as such. All who are at work in this line know with what extreme difficulty it is to carry out these bacterial examinations when several varieties of organisms are present. With regard to the staphylococcus, for instance, it grows so readily and profusely as to often cover up such bacteria as streptococci, pneumococci, or influenza bacilli, and so has been given a predominance sometimes not deserved.

Dr. Holt: Dr. Thayer has mistaken my words. I did not cite a case of recovery from meningitis; it was a case of empyema that got well. All my cases of influenza meningitis have been fatal. More than one culture will in many cases be necessary to determine the type of infection; a single culture may be misleading.

THE BASAL PRINCIPLES OF VACCINE THERAPY.

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Perhaps it is as well that the time allotted to me this afternoon only permits that I should, as it were, expose before you the broad ground plan of the territory of vaccine therapy. To criticise adequately but one of the many moot points would in itself occupy more than the given period.

Thus, therefore, in the first place, as the main basal principle it may be laid down that *bacterial infection is primarily local* and that even when the microbes spread from the primary focus, nay even when a bacteriemia is set up, there still persist tissues of election in which alone those bacteria find conditions for active growth. We may put this otherwise and say that *when bacteria gain entrance to the system they find but a limited opportunity for growth; they are destroyed in, if not by, the majority of the tissues.* Let me afford a familiar instance. Consider the course of a malignant streptococcus endocarditis. The very development of the endocardial lesions demonstrates that the streptococci have been circulating in the blood. Make blood cultures in such a case and without difficulty growths of the streptococci are obtainable. There is no question about the bacteriemia. But in such a case how rare it is to find a true abscess in the spleen, with active proliferation of streptococci in that organ. That the spleen becomes potentially infected is obvious enough: the conditions of the circulation here are just such as to filter and arrest bacteria brought by the blood, and this organ is one of the seats of election for the arrest of loosened vegetations with their mass of included germs. Infarcts are common enough, but how infrequently do these pass on to true abscess formation. The only conclusion we

can reach from this and other cases is that the splenic tissue indifferently destroys the various bacteria brought to the organ and possesses this power to an extraordinary degree. And what is true of the spleen is true also of some of the most widespread and some of the most important tissues of the body. How extraordinarily rare, for instance, it is to find abscesses developing in the skeletal muscles, in a case of bacteriemia, or in the liver, or in the brain and cord. In all these tissues the capillary network is so fine that it is impossible that bacteria conveyed by the blood do not become arrested. And here, in passing, it must be laid down that in the normal animal it is not the circulating blood that itself destroys them. If, as Briscoe has shown, bacteria be introduced into the ventricle of an excised heart, clamped at the auriculoventricular groove in such a way as to preclude clotting of the contained blood, then the bacteria undergo little or no destruction on the part of the blood: they are not even taken up by the leucocytes, or more accurately the amount of phagocytosis is minimal. Nor, again, is it the specific cells of the various tissues to any marked extent that destroy the bacteria, with the exception of the hemolymph system, and I may add as a private heresy, probably the liver. As can be seen by inoculating bacteria into the circulation, killing within a quarter of an hour and making sections of the liver and other organs, those bacteria are actively taken up and destroyed by the endothelial cells lining the capillaries of these organs.

This fact, then, that bacterial infection is primarily local carries with it the corollary that *there is a natural or indifferent or non-specific immunity toward most bacteria, exhibited in most of the tissues of the organism.* This, it is true, has its limits; it can be overcome by the exhibition (mostly under experimental conditions) of excessive numbers of bacteria, or of smaller numbers of bacteria of exalted virulence; its extent also varies as regards any particular species of bacteria in the different tissues. But I would lay stress upon it inasmuch as it has been too much neglected. It fails to be demonstrated by experiments *in vitro* and so is apt to be overlooked, nevertheless, it is of high importance in this matter of vaccine therapy.

It is the existence of this natural and cellular immunity possessed, with the limitations above noted, by most of the tissues of the body in relationship to any specific bacterial form that renders vaccine

therapy possible. Time forbids that I should discuss the most interesting and important matter of its relationship to acquired immunity.

The second great underlying principle to be recognized is that once bacteria have established themselves within a given tissue and have undergone proliferation there, that in itself is a sign that that particular tissue is not immune, that *the subsequent arrest of their growth is not due to an exaltation of the bactericidal powers of the local tissues, but is mainly due to aid contributed by the organism from without.*

This is nowadays so generally accepted that I need but indicate the main facts upon which it is based, namely, the leukocytic invasion of the infected locality on the one hand, and on the other the evidence afforded by Bier's treatment that the local proliferation of bacteria is arrested by favoring the inflow of exudate into the part. I would but call attention to Hektoën and Carlson's[1] recent brilliant and convincing demonstration that just as the natural immunity is cellular and not hæmal, so the antibacterial substances are not elaborated in the blood itself but in the tissues; that the circulating blood to which toxins have been added is rapidly deprived of those toxins and now, transfused into another animal of the same species, sets up no production of antibodies in that animal, whereas the original recipient of the toxins, although deprived of its own blood and transfused with that of a third animal, proceeds to develop immune bodies.

These are the two basal principles, but in order to utilize them, and by introducing the specific bacteria, either living or dead, away from the primary focus of bacterial growth to induce an increased antibacterial reaction on the part of the other tissues, there are certain precautions to be taken and certain subsidiary principles which must be heeded.

First, as to dosage. The fact that definite fever and malaise may accompany the development of a, to others, insignificant streptococcus papule, say, on the nose—of a local inflammation not yet elevated to the dignity of a pustule, still less to that of a good honest boil—is a clear indication that a minute growth of a not specially virulent microbe may nevertheless induce pronounced general reaction; or

Jour. Infect. Dis., vii, 1910, 319.

otherwise, minute amounts of toxines are capable, under natural conditions of setting up a profound systemic response. The fact, noted by more than one observer,[1] that the application of a minute quantity of tuberculin to the skin, slightly scarified, is adequate to induce an inflammatory reaction around tubercles of the iris, shows similarly that incredibly minute amounts of toxin gaining entrance into the circulation can produce effects, even if in this case it be in a tissue that is sensitized.

It must be kept in mind that the first serious endeavor to employ vaccine therapy dates not from Wright but from Koch, or even more accurately from Pasteur, although the latter in his method of preventive treatment of rabies sought to intervene during the incubation period rather than during the frank exhibition of the infectious disease. Koch employed at first extracts of the bacterial cultures as a therapeutic agent, so old that they contained the diffused products of dead bacilli; later, what we now are accustomed to speak of as true vaccines, namely the killed bacilli. He did not at first recognize the significance of administering minimal doses. Wright's brilliant recognition of the possibility of gauging the extent of the reaction that follows hetero-inoculation has, I am inclined to think, been of service not so much as affording an accurate index, as in affording a means of demonstrating that the best results are apt to follow inoculations of doses of vaccine so small that they need induce no systemic reaction obvious during the next few hours by ordinary clinical means. We may thus take it as a generally accepted principle that *minute rather than massive doses of vaccine are to be employed.*

As to the qualities of the vaccine, what is true regarding preventive immunization would seem to apply to therapeutic employment, namely that a more effective reaction and surer results are obtained by the employment of minute non-lethal doses of the specific bacteria, than by the exhibition of dead cultures, and by the latter than by injecting the products of bacterial growth. But inasmuch as in a frank infection we cannot consider the resistance of the organism as normal, and as, in conformity with what has already been stated, the virulence or non-virulence of a given microbe and given dose of the same is implicitly determined by its action on the normal organism,

[1] Emery, Immunity and Specific Therapy, Lond., 1909, p. 381.

so in vaccine therapy it is, in general, unwise to employ inoculations of the living bacteria. The only exception that I can call to mind is the most cautious method introduced by Williams and Webb of treating tuberculosis by inoculations of progressive increments of living tubercle bacilli, beginning with one, or a very few, accurately counted. This demands technical skill of the highest order.

So also, on general principles, it is obvious that when the various strains of not a few bacteria present wide variations in their capacity to induce the production of the various antibodies in the animals of the laboratory, *more constant results are to be gained by the employment of what have been termed autogenous vaccines*, namely, the dead cultures of the particular strain of pathogenic bacteria causing the infection in, and isolated from, the patient, rather than laboratory stock cultures. Such vaccines liberating a particular order of toxins and other bacterial products will more surely stimulate the production of just the particular order of antibodies necessary to counteract and destroy the infective microörganisms.

Next, as to what may be laid down regarding the cases suitable for this means of treatment. We may broadly express the severity of any given case of infectious disease as the difference between the resisting powers of the organism and the virulence of the microorganism. In other words, a like grade of disease is to be anticipated when the resisting powers are considerable and the virulence of the microbe also considerable, and when the bodily resistance is feeble but the virulence of the microbe also feeble. *The most hopeless cases of disease belong therefore to the categories of intense virulence of the specific bacteria, and of extreme depression of the systemic resistance.* In neither of these cases, whatever indicator we employ, whether we estimate the agglutinins, the bacteriolysins or the opsonins of the blood, do we find other than a lowering of our index of systemic reaction. *To inoculate vaccines in either order of cases is*, not to set up a reaction on the part of tissues exhausted or incapable of stimulation, but is *merely to increase the amount of toxic material circulating in the blood, and to accelerate the final event.*

Thirdly, as to the great mass of intermediate forms, what is to guide us? With Wright we may distinguish between two main groups of cases: those in which the growth of the specific organism within the

body is accompanied by a febrile state; those in which a continued febrile state is wanting, although upon occasions rise of temperature may show itself. The febrile state is the sign of diffusion from the foci of growth of the bacterial toxins, and also of the products of local tissue disintegration, and of the reaction to the same.

With Wright we accept that the non-febrile cases indicate a limited and confined local growth of the bacteria, under conditions which do not readily permit the infusion of lymph, either for the continued nourishment of the bacteria or for the conveyance of antibodies, and, coincidently, arrest the effusion of toxins and products setting up the general reaction. These conditions may be due to the tissue in which the growth occurs being by nature dense and poorly supplied with vessels, or may be of secondary development, the specific microbes being of a relatively low grade of virulence, so that the tissues immediately surrounding the foci of growth, instead of being depressed become stimulated to proliferate, whereby there is developed a surrounding capsule, well seen for example in connection with many tuberculous foci.

As we see, I might almost say daily, in the post-mortem room, in connection with obsolescent tuberculous foci, this capsule formation may be so dense that in itself it must be regarded as a means of arrest of disease, or otherwise we may reasonably deduce that there can be a grade of self-limiting infection which, as there is no general reaction, is a potential rather than an actual infection, and in which vaccination is, it might seem, unnecessary. All the same, bacteria so fenced in are not absolutely innocuous. Clinical and post-mortem room experience demonstrate that they are apt to be latent and not destroyed. It would seem that hyperæmia of the surrounding tissue and increased infusion of lymph may stimulate the bacteria to renewed growth and whether by leukocytic agency, or by necrosis and solution of the capsule, the bacteria may escape and set up active infection. The advantage of vaccination in this order of cases is that *it replaces an unprepared by a prepared organism,* and that through the sensitization of the immediately surrounding tissue it induces a very definite grade of hyperemia and leukocytic infiltration of that tissue, which, if the encapsulation is not too dense, must favor the entrance into the focus of antibacterial agencies; its disadvantage,

that owing to the process of encapsulement the prepared lymph and leukocytes percolate with difficulty into the focus and thus are apt to be presented in quantities insufficient to bring about bacterial destruction. Vaccination alone in this stage does not surely bring about cure. What is necessary is the employment of auxiliary methods promoting the freer flushing of the focus or foci with antibacterial lymph, as by Bier's methods for inducing hyperæmia or Paterson's method of graduated exercise.

Why, it may be asked, do I categorically lay down here that the lymph is the important agent? It may be well urged in objection, that owing to the contradictory results gained by different observers, one is not justified in concluding that the blood plasma and lymph, as contrasted with blood serum *in vitro*, possess either antibacterial or opsonizing properties; whereas, on the contrary, Metchnikoff has proved to the hilt that the leukocytes of an immunized animal possess far more active phagocytic properties than those of the non-immunized. Quite so. But this is to me a very striking fact that neither Metchnikoff nor any of his school have succeeded in proving that the leukocytes of the immunized animal, *per se*, the leukocytes separated from the plasma, have greater phagocytic powers than those of the non-immune animal. And this being so, we must hold as the simplest explanation that, without the influence of the immune plasma or lymph, the leukocytes are relatively inactive. Nor is it an adequate argument to urge that the leukocytes after centrifugalization and washing are depressed in their functions when placed in normal salt solution, when those same leukocytes transferred to serum will take up a score or more bacilli in a quarter of an hour. My colleague, Dr. Meakins, permits me to quote a yet more effective demonstration of this fact, repeatedly made by him, namely, the leukocytes of a highly immune animal placed in non-immune, normal serum do not take up any greater number of bacteria than do the leukocytes of a normal animal of the same species placed in the same serum.

We come now to the consideration of those cases in which the diffusion of bacterial products from the foci of growth has already caused a reaction on the part of the organism. Can we vaccinate with impunity in these cases—in the course of typhoid, pneumonia, and other acute diseases attended by manifest fever? Is there not the

danger of adding to the amount of circulating toxines, and thereby exhausting the distant tissues—lymphoid, vascular, endothelial tissue, or what not—instead of stimulating them to produce additional antibodies? Here I am inclined to lay down that the fatal event in the majority of severe infections is not brought about by exhaustion of the tissues in general, but by action of the circulating toxines upon the medullary nerve centres, and that the sign of exhaustion of the tissues or paralysis of the same and inadequate reaction on their part is a lowering and not a rise of the body temperature. Thus, in the first place, it may be laid down that to guard against excessive toxic action on the nerve centres, *vaccination should never be directly into the blood stream, but should be subcutaneous,* allowing a slow percolation of the added bacterial products into the lymph and blood; and, in the second place, that *the febrile temperature as such is the evidence of capacity on the part of the tissues to react.* This may, I think, safely be laid down, that on the one hand, *a sinking temperature accompanied by increased weakness of pulse and respiration and advancing "toxic" state, is a clear signal that the reactive powers of the patient are being overcome and exhausted,* so that vaccination can only be harmful, and, on the other hand, *if the fever be somewhat high, provided that the pulse is steady, with no signs of cardiac weakness, then vaccination may safely be undertaken.* The good results obtainable in these cases can no longer be questioned, and what is interesting is that the system evidently benefits from the slight temporary added rise of temperature which shows itself during the six hours or so immediately following the vaccination.[1] Hyperpyrexia is a contraindication.

Time forbids me to do more than note the curious paradox that often such vaccination converts a disease like typhoid that ordinarily recovers by lysis into one recovering by crisis, and, *vice versa,* time and again converts a disease like pneumonia culminating in crisis into one healing by a relatively slow but favorable lysis. I can only emphasize that the physician must be prepared for these modifications of the normal course of disease.

In conclusion, there remains to be noted what Wright, and rightly, made the guiding principle in the development of his

[1] A rise which it is interesting to note is wanting in the class of limited infections already discussed and is suggestive of increased sensitiveness of the tissues that have already been stimulated by the circulating toxins discharged from the infective focus.

methods of vaccine therapy, namely, *the establishment of an index whereby to determine the effects and course of the subsequent reaction.* This was a notable advance. Nevertheless, serviceable as it has been in establishing vaccine therapy as a rational procedure and in determining both the intervals that should elapse between vaccinations and the augmentation of successive doses, it has to be admitted that Wright's index is faulty. The principle is all important, the means of application of the same imperfect. When two of the leading experts in London, working with samples of the same blood taken before and after vaccination, can report the one that the index is raised, the other that it is lowered by the process;[1] when, as pointed out by Meakins,[2] a given serum may afford a higher opsonic index when it is diluted than when it is undiluted, and when, as noted by more than one observer[3] during a long-continued negative phase, which, according to Wright, is a danger signal, the patient may obviously be making rapid improvement, something must be wrong. The dilution method introduced by Neufeld and Hune[4] and employed on this continent by Klien,[5] Meakins and Hektoën, clearly reduces the error of the personal equation and, giving a vastly greater scale of the same order as that employed for the estimation of agglutinins and lysins, permits a comparison to be made between the opsonins and other antibodies of the serum. But if Wright's method is laborious and time consuming, this is more so. The only practical course to recommend is that, in connection with each particular infection that it is sought to treat, the observer first studies thoroughly the variations in the opsonic and other indices in a series of cases, while carefully observing the effects of the vaccination treatment at the bedside, and then, armed with this foundation knowledge of the results of different strength of doses in the different orders of cases, he educates himself to depend more and more upon clinical symptoms[6] in determining the strength and the frequency of his inoculations.

[1] E. C. Hort, Rational Immunization in the Treatment of Pulmonary Tuberculosis, London, 1909, and Brit. Med. Jour., February 13, 1909.

[2] Jour. Exp. Med., xi, 1909, 100.

[3] See Emery, Loc. cit.

[4] Arbeiten a. d. Vaiserl. Gesundheitsamte, xxv, 1907, 164.

[5] Johns Hopkins Hosp. Bull., xviii, 1907, 245.

[6] Thus, as shown by Latham (Proc. Roy. Soc. Med., Medical Section, April 1, 1909) and by Hort (loc cit.) it is possible in tuberculosis to read temperature chart in terms of the immunity curve, the latter employing not the daily variation but joining the evening temperatures into a continuous curve.

In short, vaccine therapy to be a success must be undertaken, not by the busy consultant, nor again by the confirmed habitué of the laboratory, but must be placed in the charge of one who, combining a thorough laboratory training with a certain amount of time not consecrated to other engagements, and a recognition that his future field lies in clinical medicine, accepts gladly the opportunity here afforded to apply his technical knowledge and to make intimate studies of individual cases of disease. Vaccine therapy lies in the hands of those younger well-trained physicians whom happily the foremost schools of this continent are producing in increasing numbers. Thus, as a final principle may be laid down—and I say this with a full sense of the necessity and the responsibility attaching to the statement—that vaccine therapy is not to be undertaken by the ordinary practitioner: there are too many dangers attaching thereto, and its corollary that, excellent as may be the individual preparations made by sundry firms of wholesale druggists, for them to advertise these lightheartedly, far and wide, and recommend them to the notice of the ordinary practitioner from one end of the country to the other is absolutely reprehensible, and deserves the condemnation of this Association and of all who have studied conscientiously this matter of vaccine therapy.

THE USE OF VACCINES IN TYPHOID FEVER.

By MARK W. RICHARDSON, M.D.,
BOSTON.

Two years ago, in a paper read before this Association, I had to report, after observation upon one hundred and thirty-two cases of typhoid fever as treated with specific sera, filtrates, and residues (Vaughan), that the results had been largely negative, except that by the continued inoculation during convalescence of Vaughan's non-toxic residue of the typhoid bacillus, the percentage of relapses had been cut down, apparently, from 22 to 5 per cent.[1]

Since 1908, owing to the assumption of new duties under the Massachusetts State Board of Health, I have not been able to continue my personal work on this subject. Under my supervision, however, Dr. Leslie H. Spooner has investigated the subject of so-called hospital typhoid fever, at the Massachusetts General Hospital, as occurring among the hospital personnel—house physicians, nurses, ward tenders, etc., and has introduced the use of vaccines in prophylaxis against the disease.

Dr. Spooner found, in the first place,[2] that annually for the ten years previous to 1909, from two to six nurses had contracted typhoid fever within the hospital. This was, naturally, a situation much to be deplored.

With the coöperation of the hospital authorities, therefore, the subject of protective inoculation was placed before the nurses, with the result that at the present time one hundred and twenty-five nurses, ward tenders, and physicians have submitted to antityphoid inoculation, and it seems probable that the custom will be made to apply in a routine way to all new candidates for the training school for nurses.

[1] Amer. Jour. Med. Sci., October, 1908.
[2] Amer. Jour. Public Hygiene, August, 1909.

During 1909 there were no cases of typhoid among the hospital employees. This was true, however, of the uninoculated as well as of the inoculated. Other factors, undoubtedly, helped in securing this fortunate result, such as, for instance, the compulsory use by nurses of rubber gloves when caring for patients.

The inoculations were generally three in number, at intervals of about five days. The dose began with fifty or one hundred million, and increased successively up to three hundred millions. The bacilli (twenty-four hour agar cultures—avirulent) were heated to 53° C. for one hour and suspended in salt solution with $\frac{1}{4}$ per cent. lysol. The inoculations were made on external surface of left upper arm. Local and general reactions were seldom severe. Only once was it necessary for a nurse to leave her duty for twelve hours. In two weeks blood tests showed in most cases agglutination strengths of more than 1 to 25, and in one case it was 1 to 500.[1]

This experience is, of course, simply confirmatory of that already recorded by Wright and his pupils.

It has its parallel in France and Germany, and more recently in the extended series of Dr. Russel among the United States troops.[2]

Until recently all this work has been done with dead cultures. Castellani, however, recommends[3] the use of living cultures, and these should be more effective, provided only, we may be assured of their harmlessness.

As to the use of typhoid vaccines in the treatment of the declared disease, no definite conclusion can be drawn, inasmuch as the number of cases thus treated is much too small.

Watters[4] treated forty cases with specific vaccines. The average length of fever in the uninoculated was 25.3 days. In the inoculated it was 15.5 days. The average residence in the hospital of the uninoculated was 57.6 days, of the inoculated 39.6 days. Reinfection was three times as frequent among the untreated cases.

In my personal opinion the status of vaccines in typhoid fever is somewhat as follows:

1. They are of the greatest value in prophylaxis, and should be

[1] Bost. Med. and Surg. Jour., January 13, 1910.
[2] Johns Hopkins Hospital Bulletin, March, 1910.
[3] Lancet. August 21, 1909.
[4] Boston Med. and Surg. Jour., 1910, 392.

made use of by all who, as physicians, nurses, ward tenders, or laymen are likely to be exposed to the disease. Their use by the general public cannot be expected in the near future. For this result, time and education will be required.

2. Typhoid vaccines properly used will, I feel sure, prevent a large percentage of relapses.

3. The success of vaccines in treatment of the original disease will depend upon the character of the case. Conservatively used they will do no harm and they may be of much assistance.

Early diagnosis and early treatment will be, undoubtedly, of great importance.

THE EFFECTS OF INJECTIONS OF KILLED STREPTOCOCCI.

By GEORGE H. WEAVER, M.D.,
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The effects of injections into the living body of killed virulent streptococci have been studied from two points of view: (1) as to their ability to produce immunity against similar virulent living cocci which may be subsequently introduced; (2) as to their power of bringing about in the infected body a condition of resistance which will overcome an infection already existing. Since the process doubtless is similar in each case, we may first refer to the immunization produced in the uninfected, and afterward discuss the effects of therapeutic injections in man.

It is generally accepted that the destruction of streptococci within the body is accomplished through phagocytosis. Of the antibodies which appear during immunization against streptococci the streptococco-opsonin in the blood serum has been found most important because it brings about phagocytosis of the streptococci. By estimation of the amount of such opsonin, attempts have been made to measure the degree of immunity. To be exact such estimates should be made with the virulent infecting organisms or the one used for producing the immunity. While other antibodies beside the opsonin may play a part in combatting the streptococci and their products, we have no ready method by which these may be determined. A factor which has until recently been largely left out of account in the estimation of opsonin as a measure of the ability of the body to cope with streptococcus infection is the leucocyte of the individual. Especially in infections of long standing, he relation between the bacteria and the serum and leukocytes

of the individual must be taken into consideration in estimating the ability of the individual to overcome the infecting bacteria. Rosenow[1] was the first to direct attention to this fact as regards pneumococci, and Boughton[2] has recently shown that the same is true in the case of streptococci.

Immunizing Power of Killed Streptococci in the Uninfected Animal.

In the artificial immunization of animals against streptococci for the purpose of obtaining antistreptococcus serum, it has been found desirable by some to produce a certain degree of resistance to streptococci by injecting killed cultures before resorting to injections of living bacteria. This method has succeeded in large animals as well as in rabbits. The primary injections of killed streptococci enables the animal to withstand small doses of living virulent cultures which otherwise would provoke fatal infections.

Dr. Tunnicliff and I[3] have reported some studies in streptococcus immunization in rabbits in which we showed that streptococci which had been killed by suspension in strong solution of galactose were able to stimulate the production of antibodies in a much greater degree than the same culture when killed by heat. When cultures of streptococci are heated sufficiently to kill all the individuals, the antigenic properties of the bacteria are largely interfered with. We made observations on rabbits, some receiving galactose-killed and some heat-killed streptococci in equal numbers. Following the injections the opsonin for the streptococcus was estimated. In those rabbits which had received the galactose-killed streptococci the rise in the opsonin was quite marked, while in those which had received the heat-killed bacteria the opsonin was but little affected. If, after an interval of a few days, the rabbits were injected with virulent living streptococci in doses sufficient to certainly kill control rabbits, it was found that the animals which had received

[1] The Role of Phagocytosis in the Pneumococcidal Action of Pneumonic Blood. Jour. Infect. Dis., 1906, iii, 683. Immunological and Experimental Studies on Pneumococcus and Staphylococcus Endocarditis. Jour. Infect. Dis., 1909, vi, 245.

[2] Interaction of Serum, Leucocytes, and Bacteria in Phagocytosis as Observed in a Case of Recurrent and Relapsing Erysipelas. Jour. Infect. Dis., 1910, vii, 111.

[3] A Study of Streptococcus Immunization, Jour. Infect. Dis.. 1908, v, 589.

galactose-killed streptococci had acquired a considerable degree of resistance, often amounting to a complete immunity to the dose employed, while those which had received corresponding doses of heat-killed streptococci showed no increased resistance, but often died sooner than the controls.

We know of but two connections in which injections in man of killed streptococci for prophylactic immunization have been employed on any considerable scale. Acting on the assumption that scarlet fever is due to infection by streptococci, Gabritschewsky and other Russian physicians have extensively injected killed streptococci as a prophylactic against scarlet fever. While they claim very favorable results, the observations have not been sufficiently controlled by observers elsewhere to allow of any final judgment regarding them.

Boughton and myself[1] undertook by injections of galactose-killed streptococci as early as possible in cases of scarlet fever, to bring about a sufficient degree of immunity to prevent the later streptococcus complications associated with this disease. Eighty-eight cases were injected during the acute stage. We were unable to observe any appreciable benefit from the procedure. In this case two unfavorable factors existed—the fact that heterologous cultures had to be used, and that the body was probably reduced by the disease already present in its ability to respond to the antigen

Therapeutic Injections of Killed Streptococci.

The great majority of the therapeutic injections of killed streptococci with which I am personally familiar have been employed in cases of erysipelas and in contagious diseases, especially scarlet fever. In most of the reported instances in which killed streptococci have been injected for therapeutic purposes, the bacteria have been killed by heat. In 1907 Tunnicliff and I[2] treated streptococcus infections in a case of diphtheria and in six cases of scarlet fever with heat-killed streptococci, but with no apparent benefit.

[1] The Injection of Heterologous Streptococci, Killed by Galactose, in Erysipelas and in Scarlet Fever, Jour. Infect. Dis., 1908, v, 608.

[2] Effects of Injections of Homologous Streptococci, Killed by Heat, in Streptococcus Complications in Contagious Diseases, Jour. Infect. Dis., 1908, v, 585.

When it was found that galactose-killed streptococci possessed in rabbits greater antigenic powers than heat-killed ones we undertook a study of the effects of the former in man. It was found that galactose-killed streptococci, when injected in a normal child, caused a pronounced rise in the opsonin for the streptococcus injected. This work was carried out by Dr. Boughton and myself.[1] Twenty-two cases of erysipelas were treated with injections of polyvalent, heterologous streptococci killed by suspension in 25 per cent. galactose solution, the dose being about 200,000,000 streptococci. Of these cases, 2 were relapsing, 6 migrating, and 3 recurrent. In only 3 of the series, each of the migrating form, did there appear to be any beneficial effect. In these the extension stopped within two days and recovery was rapid. In the acute stage of erysipelas there was no appreciable benefit from the injections. This was to be expected since the powers of the body were already taxed in producing the immunity which leads to recovery in the usual course of the disease. In one case of chronic nasal streptococcus infection with recurring attacks of acute facial erysipelas, a prompt and permanent cure followed the use of galactose-killed homologous streptococci. With improvement the streptococco-opsonic index rose considerably above normal and remained so for several weeks.

Thirty-one cases of scarlet fever with streptococcus complications, such as purulent rhinitis, otitis media, mastoiditis, and cervical adenitis, were given injections of galactose-killed streptococci. Of these, 11 (36 per cent.) showed prompt improvement. The beneficial effects were more marked in subacute and chronic cases. It is not unlikely that better results would have followed the use of homologous cultures in some of these cases. In a few cases the injection of killed bacteria appeared to cause an aggravation of the local infection.

As a continuation of this work, Boughton[2] undertook to treat by injections of galactose-killed homologous streptococci, cases of contagious diseases with streptococcus complications which had become chronic. In his series of 14 rather refractory cases there

[1] The Injections of Heterologous Streptococci, Killed by Galactose, in Erysipelas and in Scarlet Fever, Jour. Infect. Dis., 1908, v, 608.

[2] Injections of Homologous Streptococci, Killed by Galactose, in the Treatment of Suppurative Complications of Contagious Diseases, Jour. Infect. Dis., 1910, vii, 99.

were ascribable to the treatment 36 per cent. of recoveries, 28 per cent. of improvements, while 36 per cent. were apparently uninfluenced. In 7 cases with marked evidence of sepsis he noted prompt improvement (in one to three days) in 6, the other having been moribund when injected. In a case of recurrent and relapsing erysipelas which he treated there was no beneficial effect from the injections.

Difficulties Encountered in Judging the Results of the Injections.

In reading the reports of isolated cases treated by injections of so-called "streptococcus vaccines" one is impressed by the great difficulty of arriving at any reasonable appreciation of the value to be attached to the injections as a factor in the course of the disease. The tendency of erysipelas to run a rapid course terminating in recovery in the great majority of cases is well known. Even in patients who are desperately sick, with no special treatment, a sudden change for the better and uninterrupted progress to recovery is so often observed that one hesitates to ascribe such phenomena to therapeutic measures. In the preparation of an homologous galactose-killed streptococcus, six to eight days are required before one is assured of a sterile material for injection. It has been noticed, in routine work, that by this time about two-thirds of the cases of scarlet fever with streptococcus complications have so far improved as to require no injections. If "vaccines" had been administered in each of these cases when the preparation of vaccine was begun, they would have been placed as recoveries to the credit of the injections. On the other hand, the sudden and progressive improvement which often follows the injection of killed streptococci in cases of long standing streptococcus infection which have shown no tendency toward recovery cannot fail to impress the observer as due to some factor introduced by the injection and as not at all likely to have occurred in the natural course of the disease.

The failure of favorable results from the injection of killed streptococci in some cases of chronic infection may depend on several factors. The ability of the body cells to react and produce antibodies may have been exhausted by the prolonged course of the dis-

ease. Again, the infecting bacteria may have become so acclimated to their surroundings that they are no longer affected by the antibodies present. The interaction of serum, cells, and bacteria may be so distorted that the bacteria continue to thrive even in the presence of abundant antibodies.

CONCLUSIONS. 1. Destruction of streptococci within the body is accomplished through phagocytosis, for which opsonin is essential.

2. In estimating the ability of the individual to cope with streptococcus infections, the leucocytes as well as the serum must be taken into account.

3. Killed streptococci, when injected into an animal, may raise its resistance to living virulent streptococci.

4. It is desirable that injections of killed streptococci as a prophylactic against scarlet fever be tried under conditions favorable for control.

5. Heating interferes with the antigenic properties of streptococci. These properties are preserved when streptococci are killed by a strong galactose solution.

6. Injections of galactose-killed streptococci early in the course of scarlet fever do not prevent later streptococcus complications.

7. Injections of galactose-killed streptococci in cases of acute erysipelas and in the acute stage of streptococcus complications of contagious diseases appear not to influence the course of the disease.

8. In subacute and chronic erysipelas and in streptococcus complications of contagious diseases which have become chronic, injections of galactose-killed streptococci are sometimes followed by favorable results, and at other times no appreciable effect is seen.

9. Great caution must be observed in ascribing improvement in these cases to the injections.

REPORT OF THE INOCULATION DEPARTMENT OF THE GERMAN HOSPITAL, PHILADELPHIA.

By JOHN C. DA COSTA, Jr., M.D.,
PHILADELPHIA.

Some six months ago we began the systematic use of autogenous vaccines at the German Hospital, in the treatment of certain bacterial infections, mainly of a surgical character, yet for one reason or another either unsuited to, or unhelped by, operative procedure. For half a year prior to the beginning of this routine work, a large amount of experimentation was done, in order not to approach the large subject of vaccine therapy without preliminary training in technique and without a fair experience in observing and correlating the very important clinical data incident to this method of treatment. From the inception of this work, I have enjoyed the coöperation of Dr. John B. Deaver, Surgeon-in-Chief to the Hospital, and of Dr. A. O. J. Kelly, the Pathologist, and have been aided by the skilful services of Dr. D. B. Pfeiffer, the Assistant Pathologist.

The Selection of Cases for Treatment. Of the patients treated, the majority were examples of postoperative conditions from Dr. Deaver's wards, the others having been referred to the Inoculation Department by practitioners not connected with the German Hospital staff. In every instance the endeavor was made to select for treatment only those subjects to whom it was reasonable to believe that vaccine therapy was sanely adapted, and in these selections we were guided by consultations with the attending physician of the patient in question, by a detailed survey of the clinical history, and by the laboratory findings of the individual case. The promiscuous preparation of autovaccines from cultures taken at random, perhaps by an untrained worker, spells careless therapy and unsatisfactory results, in view of which one who does vaccine work must personally

keep in touch with the whole procedure, from the primary inoculation of the injecting bacteria to the injection of the emulsion prepared therefrom.

THE PREPARATION OF AUTOGENOUS VACCINES. In all the cases belonging to the present series autogenous vaccines were used, save in a few instances, to be referred to later, in which urgent necessity for prompt treatment did not allow the time required for the preparation of a specific emulsion. The technique employed in our work does not differ essentially from that commonly adhered to in other laboratories. Briefly, it includes the following steps:

1. Obtaining the specific infective bacteria, by suitable culturing, from the local lesion or from the blood of the patient.

2. Subculturing to obtain a pure growth, when the primary culture is contaminated with numerous types of bacteria alien to the morbid process to be dealt with. It may be noted here that only exceptionally were subcultures necessary in our series, a fortunate circumstance which saved much valuable time and simplified the laboratory end of the work.

3. Preparation of an emulsion, with normal saline solution, of the bacteria recovered by primary culture or by subculture, after its incubation for a period sufficiently long to yield a workable growth.

4. Standardizing the bacterial emulsion, so as to obtain a fixed number of germs in a given volume, a ratio of 100,000,000 to the cubic centimeter being adopted as a convenient unit for routine use. This detail of the process was carried out according to Wright's familiar method, used by him in the inoculation work at St. Mary's Hospital, London.

5. Searching stained smears of the standard emulsion for spore-bearing bacteria, whose presence must obviously forbid the use of an emulsion thus tainted, for fear of disastrous consequences from the injection of virile spores, not killed by heating the emulsion to the degree lethal to ordinary pyogenic germs But in a single instance have we been forced to abandon the preparation of a vaccine on this score.

6. Pipetting off one cubic centimeter units of the emulsion into glass ampoules, which are then hermetically sealed, and sterilizing the ampouled emulsion for sixty minutes, at 58.5 centigrade, in order

to destroy the infective principle of the contained bacteria without affecting their antidotal properties. Cultures planted from this presumably sterile emulsion of bacteria and then incubated for twenty-four hours, serve to verify the thoroughness of sterilization.

The foregoing technical steps, inasmuch as they are well known to the laboratory man, and not especially interesting to the clinician, do not seem to call for further discussion in detail.

The Use of Stock Vaccines. In the class of cases with which this report is concerned the administration of stock vaccines would have been decidedly bad practice, save under conditions of imperative necessity which demand immediate treatment. In the face of a contingency of this sort we have, on two occasions, resorted to stock emulsions, with the hope (later shown to have been a vain one) that these ready-made antidotes might tide over a crisis until an autogenous vaccine could be made, but in none of these emergencies did the venture prove successful. In certain infectious processes (notably the gonococcal) it is perfectly proper to inoculate the patient with a stock emulsion of the killed generic bacterium, but in combating streptococci, pneumococci, and staphylococci the preparation and use of autovaccines individually suited to the specific condition existing, is the only rational and reasonably certain procedure to follow. This, for the very simple reason that the inroads of a given bacterial infection can be effectually antidoted only by a vaccine indentical in race and in strain with those of the offending germs. An emulsion of, say, dead streptococci will fail to stimulate immunity in an organism teeming with live streptococci, unless both the dead injected bacteria and the live infecting bacteria happen to be of the same strain as well as of one type.

The Use of "Raw" Vaccines. When time does not allow the subculturing of a mixed growth derived from a local lesion, it has been our practice, provided that the contamination be but slight, immediately to prepare an emulsion from the primary growth in what may be termed its "raw" state; that is, without taking the time and trouble to isolate the predominant and specific bacterium, but simply using the entire mixed culture for the preparation of the bacterial emulsion. This plan has no apparent drawbacks, if the primary growth (for example, one of the pyogenic micrococci) be contaminated by a

limited number of some unidentified bacillus, and in such an event the latter may be safely disregarded, and a "raw vaccine" made, to be standardized according to its richness in known, identified germs. All of which prompts the query, "Why not habitually use 'raw vaccines,' on the premise that multiple infective agencies call for multiple antidotal principles?"

Opsonin Estimates. No use has been made of opsonin tests in this series, as an indication for inoculation and reinoculation, which were governed by more familiar clinical phenomena, relating to the subject's temperature and pulse, and to the local signs and general condition. The uncertainty of determining the positive and negative phases of the reaction seem to warrant the omission of this theoretically attractive detail, apart from the possible technical errors and from the great expenditure of time required. Some two years' experience in opsonin technique has convinced me of the uncertainty of this procedure as an accurate criterion in inoculation work. Extreme opsonin figures, high or low, are unquestionably expressive, but one is compelled to distrust values which show but trifling deviations from the normal standard, and it is such values, unfortuately, that must be interpreted so frequently in the individual instance.

Case Reports. The clinical data of this report relate to ninety-four patients treated during the past year by the Inoculation Department of the German Hospital, Philadelphia; the final results are either undecided or equivocal in forty-four of this number, still under treatment or but recently discharged. My remarks, therefore, refer to only the first fifty inoculation cases, which can be classified and spoken of with reasonable accuracy. In the selection of these patients for treatment, due weight was given to the clinical history and to the laboratory findings of the individual case, whose post-inoculative course was consistently followed until a decisive judgment was warranted. According to the character of the individual infections, the cases summrized in this report naturally fall into two main groups, as follows: (A) *General septicemia;* and (B) *Local suppurative lesions.*

Series A. *Septicemia.* This group comprises seventeen cases, of which eight died and the other nine progressed to complete recovery

from the systemic poisoning and the local factor thereof; these changes having been uniformly permanent, in so far as could be determined, by subsequent inquiry after the patients' discharge from the hospital. Nine of the foregoing series were *bacteremias*, three of them being streptococcal, five staphylococcal, and one bacillary; while in each of the remaining eight cases blood cultures were sterile, although the dominant clinical picture was that of septic intoxication. In every case belonging to this series inoculation was resorted to only after the usual surgical procedures had been practised, and in all but one instance such treatment had been attended by unsatisfactory results or by no benefit whatever.

SEPTICEMIA.

17 cases, 8 deaths, 9 symptomatic recoveries.

	Duration, symptoms	*Duration, treatment*	*Total No. inoculations*	*Inoculation, interval*	*Average dose*	*Final result*
I. *Streptococcemia.*	days	days		days		
1. Septic endocarditis	117	34	15 (550 m)	2 to 3	36 m	death
2. Septic endocarditis	27	1	1 (50 m)	—	—	death
3. Cellulitis; abscess	43	14	6 (325 m)	1 to 7	54 m	death
II. *Staphylococcemia.*						
1. Pelvic abscess	28	1	1 (150 m)	—	—	recovered
2. Renal abscess	90	30	6 (600 m)	6	100 m	recovered
3. Septic endocarditis	28	7	2 (200 m)	5	100 m	recovered
4. Cranial necrosis; abscess of scalp	21	10	3 (300 m)	5	100 m	recovered
5. Pyonephrosis	30	3	3 (300 m)	1	100 m	death
III. *Bacillemia.*						
1. Puerperal sepsis	36	4	2 (60 m)	3	30 m	death
IV. *Streptotoxemia.*						
1. Cellulitis; abscess	35	21	4 (175 m)	7	44 m	recovered
2. Cellulitis; abscess	16	5	3 (75 m)	2	25 m	recovered
3. Purulent peritonitis[1]	5	3	3 (175 m)	1	58 m	death
4. Cellulitis; abscess	1	23	4 (200 m)	4 to 7	50 m	recovered
5. Cellulitis[1]	3	1	1 (25 m)	—	—	death
V. *Staphylotoxemia.*						
1. Suppurative nephritis	21	26	13 (lb 400 m)	1 to 6	108 m	death
2. Suppurative phlebitis	17	22	5 (650 m)	4 to 7	130 m	recovered
3. Appendicular abscess	3	12	4 (400 m)	3	100 m	recovered

SUMMARY.

	Cases	Deaths
Streptococcemia	3	3
Staphylococcemia	5	1
Bacillemia	1	1
Streptotoxemia	5	2
Staphylotoxemia	3	1
	17	8

[1] Stock vaccine inoculations.

Bacteremias. The three *streptococcus bacteremias* (Cases VI, VII, VIII) died. The first (Case VI) was one of *malignant endocarditis* with multiple deep abscesses, and crippled by a profound sepsis of one hundred and seventeen days' duration. Fifteen inoculations (totalling five hundred and fifty million streptococci, recovered from the patient's blood) were used, without any more definite effect than a transient improvement, succeeded three weeks later by death. The second fatal case (Case VII) received but a single injection of fifty million hemal streptococci, twenty-four hours before death; this patient, septic from a large *subpectoral abscess* and purulent cellulitis, was virtually moribund when he received the vaccine, which was given without any real belief in its power to combat such an overwhelming toxemia. The third fatal case in this class (Case VIII) had been ill forty-three days with *malignant endocarditis*, complicated by toxic nephritis, and subsequently developed extensive pelvic thrombosis. Six injections, totalling three hundred and twenty-five million cocci of hemal origin, were given, without any lasting benefit, during the fortnight preceding immediately the subject's death.

Of the five *staphylococcus bacteremias*, one died, an example of *postoperative sepsis* following nephrectomy for pyonephrosis of the right kidney. This patient, after a thirty-day period of sepsis, was given three daily injections of one hundred million staphylococcus aureus autovaccine, derived from a blood culture; but the prostration, already alarming, became even more desperate, and death occurred within nine days, without any sign of reaction to, or benefit from, the inoculations. The four staphylococcus bacteremias which recovered (Cases I, II, III, and XI) were incident to *malignant endocarditis*, and to *abscess* of the *neck*, the *kidney*, and the *ovary*, respectively. The first case is peculiar in that both the blood and the pelvic pus contained a pure culture of staphylococcus albus, a coincidence which seemed to justify a presumption that the blood-culture did not stand for a contaminating skin coccus, which presumption was later verified by the prompt recovery of the subject after having received one hundred and fifty million of a hemal staphylococcus autovaccine. Details of this interesting case-history, along with those of the three staphylococcus aureus infections of this group, will be given in a later report.

The single example of *bacillemia* (Case XIII) died, from the inroads of a *puerperal septicemia* lasting thirty-six days, after having received thirty million autogenous bacilli on the thirtieth and on the thirty-third days of her illness. The vaccine here employed was made from a growth obtained from the patient's blood, which contained bacilli culturally indentical with the *B. endocarditidis*.

Toxemia. Of the three fatal *toxemias*, two were of streptococcal origin, and the other one of staphylococcal. These two *streptotoxemias* were the only instances in this series in which a stock vaccine was employed, this makeshift step having been prompted by the urgent demand of the circumstances, which forbade the delay necessary for the preparation of an autogenous vaccine.

In the first case (Case XV) there was intense sepsis due to purulent peritonitis, with laparotomy three days before death, and vaginal puncture three days earlier. The patient received three daily injections, aggregating one hundred and seventy-five million bacteria, of a stock streptovaccine, during the last seventy-two hours of her life, and also 80 c.c. of antistreptococcus serum, but without the slightest beneficial result from either. Blood cultures were sterile, but the pelvic pus swarmed with streptococci, which finally developed on blood-agar. too late to be used for the preparation of a vaccine.

In the second fatal case (Case XVII) a single injection of twenty-five million laboratory streptococci was given, without definite effect, three days before his death, to a man of sixty-three years, prostrated and delirious for the preceding four days from intense sepsis following an infection (streptococcal) of the hand and arm.

The fatal *staphylotoxemia* (Case X) associated with a suppurative nephritis, was of three weeks' standing, and ran its course wholly uninfluenced by autovaccination, and despite nephrectomy of the pus-riddled organ. In all, one billion four hundred million autogenous cocci were given, in doses of from fifty million to one hundred million, and at intervals of from one day to six days, according to the prevailing clinical demands. A pure culture of staphylococcus aureus, recovered from the renal pus, was the basis of the vaccine prepared and used in this hopeless case.

Of the five toxemias which recovered, three were streptococcal

(Cases XIII, XIV, and XVI), and two staphylococcal (Cases XI, XII). All of the streptotoxemias were met with in connection with purulent and cellulitic processes of the extremities acquired from infected wounds distal to the chief inflammatory foci. The two favorable staphylotoxemias were associated with purulent phlebitis and with periappendicular abscess, respectively. In none of this group of five septic intoxications could there be any question as to the curative effect of the autovaccine upon both the systemic and the local phenomena.

SERIES B. *Local Suppurative Lesions.*

From this collection of some seventy-odd cases, thirty-three can be analyzed correctly, and, for clearness, may be classified thus:

		Cases
Group A.	Furunculosis	13
Group B.	Carbuncle	9
Group C.	Suppurative otitis	11

The remaining suppurative processes still under treatment or observation form a fourth Group (D) and will be detailed in full in a subsequent article.

Furunculosis. Nine of the thirteen patients treated made apparently perfect recoveries, after having received from two to eleven inoculations, each averaging one hundred and fifty million cocci. In two instances absolute failure occurred; and in two there were repeated relapses after disappearance of the lesions first noted. All of these furunculosis group were of staphylococcal type (ten albus, and three aureus), and the clinical picture ranged from a limited furunculosis of the neck to disseminated abscesses of the trunk and the extremities.

Carbuncle. Seven of the nine carbuncles showed prompt separation of the slough, thinning of the discharge, and rapid granulation after inoculation. In two cases the lesion spread, and was finally cured by the knife. All of these processes also were of staphylococcal origin, albus in five and aureus in four. The dose of vaccine was virtually the same as that used in furunculosis, but the number of inoculations was distinctly less, ranging from one to four.

Suppurative Otitis. Of all the local suppurations dealt with, this disease proved the most resistant and stubborn, although an occasional brilliant result from a minimal dose of vaccine was observed.

In six of our eleven cases the ear-discharge had been absent for from six weeks to twelve months after inoculations were discontinued. In two cases erratic relapses were noted; and in three there was no improvement whatever. The average course of treatment lasted forty-one days, and the total dosage, in favorable cases, ranged from fifty million to two billion, six hundred million bacteria.

Conclusions. Analysis of the foregoing data, correlated with the individual case-histories, suggests the following conclusions as to the utility of vaccine therapy in bacterial infections:

Autovaccines are of distinct service in the treatment of general septicemia, especially in postoperative cases in which surgical measures have been inadequate. Vaccines are useless in combating a sepsis so intense as to stifle resistance, and in such instances the clinical severity of the infection, rather than the identity of the offending bacteria, is the criterion of prognosis. The precise utility of vaccines in this class of diseases cannot be accurately fixed until additional statistics are available.

From a laboratory viewpoint, the prognosis is better in toxemias than in proved bacteremias (37 per cent. *vs.* 55 per cent. mortality). The outlook is hopeless when streptococci invade the circulating blood.

Autovaccines produce the best results in local infectious lesions. As a rule, furunculosis, carbuncle, superficial and deep abscess, infected sinus, and similar processes yield promptly to appropriate vaccines, the effect of which is generally permanent, if permanency be judged by a lapse of several months without recurrence. The duration of an immunity thus acquired must, of necessity, vary greatly in the individual case, and therefore cannot be expressed in definite terms.

The use of stock vaccines is bad practice in dealing with the class of infections under discussion. Autogenous emulsions invariably should be employed, save when some acute emergency calls for the immediate use of a stock preparation, in the meager hope of tiding over a crisis.

The opsonic index cannot be relied upon as an indicator for inoculation and reinoculation, which should be governed by the general condition of the patient and by the local signs.

The best results follow the administration of a moderate initial dose of vaccine, with subsequent doses of greater potency. A "moderate dose" of streptococci varies from, say fifteen to twenty-five million; and of staphylococci, from fifty to two hundred million. Experience has taught that an interval of from three to seven days between inoculations is usually satisfactory.

The longer one's experience with inoculation work, the more keenly one must realize how imperfectly the true scope and limitations of vaccine therapy are understood.

The utility of autogenous vaccines to set up a specific immunity cannot be questioned, but this is inadequate, in dealing with a septic condition, which presumably may be attended by widespread cell destruction, excited by the action of cellular ferments. *No vaccine, however potent, can successfully combat this ravage*, and to this fact it seems reasonable to attribute our utter failure to cope with certain grave infections by the aid of bacterial inoculation. Under such circumstances one must also recall the possibility (be it near or remote) of aggravating the anaphylaxis of an organism saturated with toxic material.

RESULTS ON VACCINE THERAPY.

By WILLIAM H. PARK, M.D.,
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Although bacterial vaccines have been used for several years in the treatment of different diseases excited by bacteria, there still remains much doubt in the minds of most observers as to the extent of their value and as to the infections in which they are most useful. As my brief remarks follow those of four other speakers, I will largely restrict them to the discussion of some points not touched on by them and to impressions derived from personal observations. No one has mentioned one reason why we might expect in septicemia the subcutaneous injection of vaccines to produce antibodies, when the bacteria causing the disease do not do so. We know that when bacteria or their specific poisons are mixed with an excess of their respective specific antibodies they unite with them and are so changed as to no longer produce antibodies when injected into healthy animals. The use of toxin-antitoxin mixtures well illustrates this. A small percentage of antitoxin robs the toxin of its poisonous properties, but leaves to it its power of producing antibodies, while a larger amount robs it of all power to stimulate the cells to produce an antitoxin.

As you are all aware, when antibodies are present in the body they are in a much greater concentration in the blood than in the tissue fluids. When, therefore, bacteria are in the blood in an infection of some duration they are in contact with their antibodies and probably combine with them to an extent sufficient to prevent their acting as a stimulus to the further production of antibodies. If these same bacteria were introduced into the subcutaneous tissues they would not be neutralized in this way and so prevented from

causing a production of antibodies. Experimentally we have proved this by injecting rabbits with bacteria which have been sensitized by placing them in immune serum. These sensitized vaccines have not produced antibodies. We have also injected bacteria into the blood of highly immunized animals and have obtained no further accumulation of antibodies, while subcutaneous inoculations of the same amount of bacteria into other highly immunized animals have produced a large increase.

There are a number of practical points which the physician should know about the preparation of vaccines which have not been touched upon by the previous speaker. They must be heated in order to prevent danger of infection, but this heat should not be above 58°, and should better be about 56°, in order that the proteids should not be altered. Suitable antiseptics, such as one-half per cent. of carbolic acid, may be used instead of heat. Bacterial vaccines retain their value for several months without appreciable alterations, and may be used after many months when fresh cannot be obtained. The bacteria used may be either derived from the case itself, when they are called autogenous vaccines, or they may be derived from the laboratory cultures, when they are called stock vaccines. I do not agree with those who object to the use of stock vaccines in all kinds of infection. It is frequently overlooked that all the treatment with vaccines made from tubercle bacilli has been and must continue to be with stock vaccines. On the other hand, such organisms as streptococci, pneumococci, and colon bacilli, which have a number of varieties, generally give better results with autogenous vaccines than with stock vaccines. A good rule is to get autogenous vaccines when we can, but when that is impossible to use stock vaccines.

The interval and size of dosage is still under active investigation and different authorities advise different methods. Many prefer to give daily small doses, others give larger doses every two to seven days. It is too early to decide which is the better method. My personal preference is to make the intervals short, certainly not longer than three or four days.

The cases which are most suitable for vaccines seem to me to be those that are localized or that have become subacute or chronic.

Most observers agree that an acute progressing septicemia, a severe typhoid infection or an acute meningitis is but little influenced by vaccines, and only when generalized infections become subacute is there a probability of a good effect.

The results of vaccine treatment so far as I have observed them have not come very quickly or been striking. There may be a slight betterment after the first, the second or the third injection, but at other times this improvemnt is delayed until ten or twelve have been given. Those cases which appear to show immediate striking benefit have always left me in doubt as to the cause of the improvement. You remember how two years ago, before this Association, Dr. Potter described two cases of septicemia, one of which received vaccine and the other did not. Both made a striking recovery. If he had not been prevented from giving the vaccine to the second case, it would have seemed as almost certain that the vaccine had produced the cure.

My own observations have been limited to the use of vaccines in the treatment of tuberculosis, gonorrhœal arthritis, vaginitis and glanders, various staphylococcus infections, streptococcus septicemia and streptococcus complications of scarlet fever. The results in a considerable number of cases of gonorrhœal vaginitis treated by us have been rather doubtful. In other hospitals, however, where the same stock vaccines were used much more striking results were thought to be obtained. We treated only alternate cases, while they treated every case. The symptoms in the treated cases have abated on the average a little more rapidly than in those not treated, but the infecting organisms have remained for about as long a period. The results in chronic gonorrhœal arthritis while slow in appearing have apparently been good. Two out of three cases of subacute glanders treated with vaccines recovered.

In the scarlet fever wards of the Willard Parker Hospital, Dr. Huddleston has treated a number of cases who had inflamed joints with streptococcus vaccines, with doubtful benefit. The staphylococcus infections which we have treated have yielded us as well as others the best results. In two cases of persistent development of crops of very severe boils the injections brought about a cure, and whenever new boils threatened they were aborted by a repetition of

the injections. The use of vaccines derived from tubercle bacilli have apparently done good in incipient and arrested cases. Our results in a few cases of pneumococcic and streptococcic septicemia have been indefinite. I believe a correct estimation of the results of vaccine treatment would be arrived at more quickly if it were possible to frequently control treated cases with similar infections not treated, so that we might obtain a correct impression of the difference produced by the injections. Even then it will undoubtedly be a number of years before we will clearly appreciate the class of cases which vaccines will benefit, and those which they will not. Probably only the observations made by especially trained men will ever give us this correct impression.

DISCUSSION.

Dr. Frank Billings: From the physician's point of view I should like to add a word or two. We have used vaccination in various forms of infections at the Presbyterian Hospital, in Chicago, with satisfactory results in a certain class of cases, and very unsatisfactory results in others. I was glad to hear Dr. Adami's paper because the principle laid down by him confirms our results. In acute infectious diseases with severe clinical course, as in pneumonia, typhoid fever, and especially in forms of chronic infectious endocarditis, vaccination seems to do certainly no good, and may do harm. I think that in those patients suffering from chronic infectious endocarditis we have a good example of the statement made by Dr. Adami, that the exhaustion of the patient is so great that no further antibodes are formed, and, therefore, harm is done by vaccination. In such patients the use of vaccination is certainly to be deprecated. They go on to a fatal termination, having been made worse by vaccination or inoculation. In certain chronic forms of infections, however, a great deal of good may be done. Here is a principle which must be carried out if the vaccination is to do good. Take, for instance, the genito-urinary tract; if there is a morbid anatomical condition of the kidney, or the ureter, or the prostate, or if there is a pelvic condition in which there is a distortion of the bladder and poor drainage, one can continue vaccinating forever and not drive the organisms out; but if the physical condition can be overcome, vaccination may cause them to disappear. The colon bacillus is a frequent inhabitant of the urinary organs; in the majority of cases they exist there without producing any symptoms; occasionally they take on, however, pathogenic properties, especially when there is some morbid lesion present in the genito-urinary tract such as a cystitis, a pyelonephritis, or other morbid condition. With the

colon bacilli we find a mixed infection very often, with, especially, tuberculosis of certain parts of the genito-urinary tract. When the colon bacilli exists with the tubercle bacilli, it then is sometimes a source of sepsis. When vaccination is used, it may drive out the colon bacilli, and then the patient may suffer less from the genito-urinary symptoms. In some forms of infection of the genito-urinary tract, like that from the proteus, there will be no favorable results from the vaccination, even when surgery is done. All this holds true in infections of other cavities of the body. One may vaccinate for ever and ever with the typhoid bacterium when there is a typhoid infection of the gall-bladder. I have tried it in two cases and without results. In infections of the antrum, unless properly drained, vaccination is of no value. If once, however, the infecting focus is drained, then vaccination is of value. If one has a chronic infection of one organ, say the tonsil, and such a tonsil has been sealed over by a previous tonsillitis, closing the seat of infection, it is useless to vaccinate. The fecal infection must be surgically removed.

Another clinical point is this: In many of these chronic cases, in addition to vaccination, the patient is permitted to go about and no result is obtained; but place such a patient at rest in bed, so fortifying the body, and this, plus the vaccination, frequently will result in cure.

Dr. Francis P. Kinnicutt: At the last meeting of this Association there were reported several cases of streptococcus bacteremia associated with endocarditis in which recovery occurred under the administration of autogenous vaccines. We have been carrying on this work at the Presbyterian Hospital with varying results. In the last three weeks we have received into the wards of the Presbyterian Hospital 3 severe cases of puerperal sepsis, 1 of an exceedingly acute nature. In all of them autogenous vaccines (streptococcus bacterium) were prepared in the laboratory and infused; these cases recovered. In one case particularly the symptoms were very severe. This patient had a temperature of 106° F., and it remained high for several days in spite of the vaccines; the systemic resistance was exceedingly feeble. On admission the leukocyte count was only 9000; it fluctuated between 9000 and 11,000 until the vaccines were used; within one week the count rose to 20,000, then to 25,000 and to 30,000, associated with marked improvement in all the symptoms. Complete recovery followed, the leukocyte count, gradually becoming, and remaining, normal. It seems to me, in view of similar reports made from time to time in cases of acute sepsis, that the autogenous vaccines must be regarded of much value. In our cases we have followed the suggestions made by Dr. William H. Park. A polyvalent serum was used until we could procure an autogenous vaccine, which was then substituted.

TRICHINOSIS.

A CLINICAL STUDY OF FIFTY-TWO SPORADIC CASES.

By W. GILMAN THOMPSON, M.D.,
NEW YORK.

Since the accidental discovery by Frederick Albert Zenker in 1860 of the *Trichina spiralis* as the cause of serious endemics of disease, such endemics and sporadic cases have from time to time been reported in the United States, but trichinosis is usually referred to in the literature as a rarity, and the reports of cases are often so superficial as to argue lack of familiarity with the disease. The fact that I have been able to obtain records of fifty-two sporadic cases occurring during the past six years (observed in my personal practice and in the service of colleagues and myself in the Presbyterian and Bellevue Hospitals) proves that trichinosis is much more common as a sporadic disease than is usually supposed—at least in the vicinity of New York where there are so many emigrants whose dietetic habits render them liable to infection.

In New York City the Meat Inspectors of the Department of Health direct their examinations mainly to the detection of tuberculous meat, and no systematic microscopic examination is made of the various products of swine flesh.

Owing, moreover to the frequency with which I have found demonstrable trichinosis unsuspected or wrongly diagnosed, it is my belief that sporadic examples of the disease are much more prevalent than is generally supposed. The following analysis of the fifty-two cases may serve to emphasize the importance of this subject.

In trichinosis the onset of symptoms is acute, either in the form of sudden chills or muscular pains, with vomiting, severe frontal head-

ache, prostration and fever. In a majority of the cases in which the date of infection could be fixed definitely, the onset took place after two weeks' incubation, the extremes being nine days and three weeks. In some cases after an acute onset the patient was better, perhaps able to return to work, when in a few days prostration again overtook him.

The vomiting, which is an early symptom in the more severe cases, may be accompanied by intense abdominal cramps and contractures of the leg muscles.

Diarrhea is by no means a constant symptom. I have remarked it as an immediate symptom in several patients who had eaten tainted swine flesh, when it appeared due rather to ptomaine poisoning (botulismus) than irritation by the trichinæ. As a later symptom it characterized about one-fifth of the cases. Others exhibited constipation throughout, or constipation alternating with occasional diarrhea. Tympanites was often present and in one case there was hemorrhage from the bowel. Repeated search for trichinæ was made in the stools and blood of the patients, but they never were discovered.

Distinct chills or indefinite rigors were present in about one-fourth of the cases, usually occurring within the first few days of the disease. The chills were followed not infrequently by sweating, and profuse sweats were common throughout the grave cases.

Erythema was often manifest in the face and neck, sometimes also over the body. I have not noticed the general pruritus referred to by one or two writers, but have once or twice observed herpes labialis, urticaria and a macular eruption on the abdomen, not unlike the roseola of typhoid fever.

In one of my cases serious epistaxis occurred.

In all the more severe cases there was early complaint of great muscular weakness and prostration, while sometimes, but by no means uniformly, there was loss of weight. One patient of the series lost fifteen pounds. As a point of distinction from typhoid fever, the loss of weight is not usually commensurate with the extent or duration of the temperature in trichinosis.

The *muscle pains* and tenderness are usually very general and severe, but in many cases the pains were most intense in special

groups of muscles, especially in the arms, calves of the legs and thighs. Tenderness over the diaphragm was common. In exceptional cases the muscular pains and tenderness were so slight as to be very little complained of, at least at the time when the patient came under observation. In such cases the trichinæ are probably already firmly encysted.

The eye symptoms were interesting. Severe pain and burning sensation in the eyes was usually complained of, and was distinctly localized independent of the headache. I have seen three cases in which there was circumscribed corneal hemorrhage, bilateral and close to the iris, which probably was due to local irritation by the trichinæ.

In one additional case only was vision affected temporarily. There was an optic neuritis with edema of the retina near the optic nerve, and small hemorrhages in the macular region of the left eye, while the fundus resembled that of acute nephritis. From time to time small fresh hemorrhages appeared in both eyes, but the process entirely cleared up.

F. J. Parker[1] reported several cases from the Presbyterian Hospital Dispensary, among which were four with tenderness of the eye globes on pressure, diplopia and pain on rotation. In four cases there was conjunctivitis, and in one neuroretinitis with edema and hemorrhages of the retina. In two there were subconjunctival ecchymoses.

C. Staubli[2] reports a case with subcorneal ecchymosis and Kratz observed this symptom in eight patients in an epidemic of 264 cases in Hedersleben. Dilatation of the pupils has also been recorded.

Edema of the eyelids was present in one-fourth of the cases of my series, at some time during their course. It may be so slight as as to escape the patient's notice, or severe and accompanied by swelling of the cheeks and forehead, so as to make the face resemble the appearance in acute nephritis.

Edema of the ankles was common, and sometimes there was swelling about such major joints as the knees and elbows, an appear-

[1] Med. Record, August 3. 1907, p. 179.
[2] Monograph, "Trichinosis," Weisbaden, 1909, p. 59.

ance which often has led to a mistaken diagnosis of rheumatism. The edema occurs irrespective of the localization of pain.

Cough was present in a number of cases, with slight bronchitis, probably due to irritation of the bronchi by the parasites, but the latter were not found in any of the sputa examined.

Dyspnea was a very common symptom but it was usually objective rather than subjective and unaccompanied by pulmonary signs or cyanosis. It often appeared to be due to invasion of the diaphragm muscle by the trichinæ, for in such cases the abdomen was markedly sore and the type of breathing thoracic. The maximum rate of breathing observed in any case was 60, and in a number of cases it reached 36.

The urine as a rule presented few abnormalities, but in some cases scattered red blood corpuscles and a trace of albumin were observed. In one patient a subacute nephritis developed and in a case seen in consultation there was an acute hemorrhagic nephritis with excessive hemoglobinuria. In this case, however, the urine was also "smoky," as in carbolic acid poisoning, and the patient had been drugged with an excess of potassium iodide and salicylates, in the mistaken belief that he was suffering from obstinate rheumatism. Micturition sometimes is painful. A positive diazo reaction frequently was obtained. The leukocytosis, as a rule, was not excessive, and apparently never as high as it may be in many purulent infections, pneumonia, gas poisoning, etc. In one-third of the cases it was not above 15,000, and in only 3 cases was it above 32,000, the maximum being 40,200. Polynucleosis varied from 28 to 87.5 per cent. The lymphocytes varied from 4 to 20 per cent.

Attention was first called to the high percentage of eosinophiles in the blood of patients having trichinosis by the researches of W. S. Thayer and Thomas R. Brown,[1] and it has proved of great diagnostic importance. This percentage was above 20 in 31 cases, or considerably more than half of my series. It was above 40 in almost one-fourth of the cases, and the highest records were two cases giving 60 per cent., one 52, one 74 and two 81 per cent. In one of the latter the full blood picture was as follows:

[1] Lancet, 1897, and Jour. of Exper. Med., 1898, No. 3

Polynuclear cells	14
Large lymphocytes	1
Small lymphocytes	3
Large mononuclear	1
Eosinophiles	81
	100

In another case with phenomenally high eosinophilia the blood picture showed:

Polynuclear cells	28.6
Transitional cells	0.0
Large mononuclear cells	0.0
Lymphocytes	11.4
Basophiles	0.0
Eosinophiles	60.0
	100.0

In another case there were 28,750 leukocytes with the following differential count.

Polynuclear cells	16.5
Lymphocytes	5.5
Transitional	4.0
Eosinophiles	74.0
	100.0

In repeated examinations in this case the eosinophiles rose in number as the leukocytosis declined. C. Staubli noticed this relationship in experimental trichinosis in animals.

In an experimental research in guinea-pigs, this author[1] produced eosinophilia of 52 per cent. with artificially induced trichinosis and Kerr[2] reported a case in man with 86 per cent of eosinophiles.

T. H. Dexter[3] reported cases with eosinophilia up to 68 per cent. H. Albert and H. W. Norris[4] reported a case of trichinosis with an eosinophilia of 72 per cent. J. L. Hirsch[5] reported a house endemic of 5 cases of trichinosis in one family from eating raw ham. In one of these cases there was 45 per cent. of eosinophiles, and in none was the eosinophilia definitely related to the severity of the symptoms In one of the 5 cases of trichinosis reported by Thomas R. Brown[6]

[1] Monograph on "Trichinosis," Weisbaden, 1909.
[2] Phila. Med. Jour., August 25, 1900.
[3] New York State Jour. of Med., March, 1910, vol. x, No. 3.
[4] Jour. Amer. Med. Assoc., November 21, 1908.
[5] Ibid., January 15, 1910.
[6] Med. News, January 7, 1899.

the eosinophilia reached 50 per cent., and in another, 49 per cent. The eosinophilia sometimes presented considerable fluctuation during the progress of the disease. Thus in one case of my series the count fell from 33 per cent. to 7.5 and rose again to 12 per cent.

The eosinophilia affords no accurate index of the severity of the symptoms, either as to fever, muscle pains or otherwise. For example, in one case the eosinophilia was 74 per cent., while the temperature was only 102° F.

One of the most protracted and serious of my cases gave the following blood count (made by Thomas W. Hastings): Leukocytes, total 10,000; polynuclear cells, 70 per cent.; lymphocytes, 20 per cent.; eosinophiles, 12 per cent. At this time the patient's temperature was 105° F. While he was convalescing, with normal temperature and no pain or tenderness, the eosinophilia rose to 62 per cent. In another case the eosinophilia numbered only 28 per cent., while the temperature was, 105° F. In one case the eosinophiles numbered only 3 per cent. at the time when trichinæ were obtained from the gastrocnemius, although they had previously numbered 10 per cent. at the onset and 24 per cent. subsequently.

In another case the eosinophilia, which was 30 per cent., while the temperature was 104° F., rose to 52 per cent. after the temperature had been normal for ten days. As the eosinophiles accumulate around the encysted trichinæ their percentage may vary with the site from which blood is obtained for examination. For example, in one case blood from the infected muscle area gave 59 per cent., but that from the ear lobe (which was not tender) yielded only 33 per cent. I have been unable to obtain data as to the duration of the eosinophilia after recovery, for the patients usually being well, pass from observation, but one man went home in good health still showing 62 per cent. of eosinophiles, and K. Schleip reported 45.2 per cent. in a convalescent.

Various theories have been advanced regarding the function of eosinophilia. Bazzicalupo[1] discusses the connection between eosinophiles and anti-bodies in serum with the conclusion that they bear direct relation to the presence of toxins in the blood, being

[1] Gaz. degil Ospedale, Milan, vol. xxix, No. 35.

in inverse relationship to the production of antibodies. There are, however, so few diseases of pronounced toxemia in which eosinophiles are notably increased, that their role cannot be very important. They have been found increased under the following conditions: (1 to 4 per cent. being normal in adults):

1. In pneumonia, just before the crisis, exceptionally, 5 or 6 per cent.

2. In a few skin diseases of wide distribution such as: dermatitis exfoliativa, pemphigus, psoriasis, prurigo, general eczema, such bullous eruptions as dermatitis herpetiformis and in leprosy, in all of which they rarely reach 10 or 12 per cent., and do not long remain at that ratio. J. C. Johnston and Hans J. Schwarz report from the Cornell University Medical College Clinic[1] a case of dermatitis herpetiformis with eosinophilia of 9.6 per cent., and one of prurigo of Hebra with 21 per cent., subsequently falling to 2.6 per cent. No mention is made, however, of the exclusion of possible intestinal parasites as a complication, and in another of their cases of prurigo the eosinophilia was only 3 per cent. In trichinosis, however, the eosinophilia is not only *invariably* present, but usually in high degree and remains long.

Thomas R. Brown found 24 per cent. of eosinophiles in a case of chronic eczema, and John W. Coe[2] found 51.8 per cent. in a case of pemphigus, 21 per cent. in one of psoriasis, 20 per cent. in one of dermatitis herpetiformis, and 18 per cent. in one of psoriasis. In all such exceptional cases, however, the diagnosis is of course obvious from the presence of the cutaneous lesion, but care should be exercised to exclude the possible coexistence of intestinal parasites of some kind. Moreover, in cutaneous cases of equal severity, eosinophilia is by no means constant. For example, in a second case of pemphigus studied by Coe, it was absent.

3. With intestinal parasites (other than trichina spiralis). The eosinophilia accompanying uncinariasis, round worms, tape worms of various species, and other intestinal parasites is rarely very high and never so high as in most cases of trichinosis. I have seen it 2.3 with tænia saginata and only 1.5 with ascaris.

[1] New York. Med. Jour., March, 1909.
[2] Presbyterian Hospital Reports, New York, 1904.

4. In bronchial asthma. In an obstinate case of the latter disease which I have lately observed in a girl, aged twenty years, the eosinophilia during a paroxysm reached 12 per cent. Repeated examination of the stools failed to reveal evidence of any form of intestinal parasite and trichinosis was positively excluded. Thomas R. Brown cites a case of bronchial asthma with an eosinophilia of 22.4 per cent.

Ira S. Wile,[1] in a general study of eosinophilia, says that a moderate increase in eosinophiles may be produced exceptionally by such drugs as camphor, potassium iodide and sodium salicylate, but I have never observed it even where large doses of these drugs were being administered. He also claims that improvement in tuberculosis is accompanied by eosinophilic increase.

Microscopic examination of sections of muscle were made in various cases of this series from such muscles as the deltoid, biceps and gastrocnemius. In 29 cases trichinæ were found, and in 5 more an acute myositis was present. In the remaining 18 cases either no examination was made, or no trichinæ were found in the epecimen isolated, but in all these cases the other symptoms, such as a high grade of eosinophilia, puffiness of the eyes, dyspnœa, fever and generalized muscular pains and soreness, justified the diagnosis, especially as such cases frequently occurred in connection with one or two others in which the trichinæ were found, *i. e.*, among patients simultaneously exposed to infection.

In one case the fragment of biceps muscle examined by Dr. Meakins of the Pathological Department of the Presbyterian Hospital, showed the encapsulated spirillæ lying between the muscle fibres, each surrounded by a zone of eosinophiles. In two cases small round-cell infiltration of the muscles was recorded and in another there was infiltration with round and polygonal cells together with eosinophiles. Another case presented between the muscle fibers, minute cysts with dense granular contents.

The temperature rise is one of the most interesting symptoms. It is fairly acute and varies from a few days to several weeks in duration—in the longest case of the series ten weeks, in the shortest, three

[1] Med. Record, January 29, 1910.

days. In the ordinarily severe cases it remains at a maximum of 104° to 104.5° F. for four to five days, when it declines gradually, with daily fluctuations of about 3° F.

The subsidence is always by lysis. In average cases the temperature consumes from ten to sixteen days in falling from 104° F to normal, but not infrequently, after falling to 100° or 101° F., it remains constant at that low level for many weeks. In one case a temperature between 100° and 100.5° F. lasted ten weeks. In another case the temperature ranged between 101° and 100° F. for forty days, and a large number exhibited more or less fever for six weeks. In twenty cases of the series the temperature passed the 104° F. record, in three it was 105° F. and in two, 105.5° F. In more than half of all the cases it rose considerably above 102° F. Despite the high and often protracted fever, the patients usually appear much less ill than with similar grades of fever due to other causes and are rarely delirious. One of my patients presented a temperature of 105.5° F., an eosinophilia of 62 per cent., and trichinæ in the muscle fragment removed, yet the man had comparatively little muscle soreness throughout, and felt so well at the height of the fever that it was with difficulty that he was persuaded to remain in bed.

In a few cases—four or five—after an interval of three or four weeks of apparent recovery, there was a return of symptoms, and in several there was a decided exacerbation of temperature and other symptoms after their partial decline. As a rule, however, inprovement once begun, progresses uninterruptedly although very slowly.

The nationality of the patients included a wide range. The majority naturally from their dietetic habits were foreigners, such especially as natives of Hungary, Poland, Norway, Bohemia, Germany, Austria, and Italy, but not a few were Americans. Six of the private patients whom I have seen were Americans in good social position, victims of infected sausage and potted ham. The previous diet of those patients who could give an intelligent account of it after the long intervening latent period had elapsed, included such foods as raw pork, raw ham, potted ham, imperfectly smoked ham, head cheese and a variety of sausages.

Albert and Norris, in the article above cited, report an endemic of

14 cases of trichinosis occurring in 1908 in Grinnell, Iowa, from eating imperfectly boiled ham.

The disease as met with in this country is rarely fatal, although the patients may become very seriously ill. There were only two deaths among the entire series of cases herein presented. One of these occurred in a Pole in my service who had only 5 per cent. of eosinophiles while trichinæ were discovered in the deltoid. He acquired erysipelas and pneumonia which, rather than the trichinosis, were the cause of death. The other patient, the only one in whom the disease may rightly be said to have been the cause of death, died in delirium with respirations of 60, a pulse of 132, dry tongue and high fever. In this case the maximum eosinophilia was 14.5 per cent.

That the eosinophilia of trichinosis which is unique in its excess is due to some specific toxin generated through the agency of the parasite might be argued from the fact that in acute or subacute polymyositis, unattended by trichinosis, it is absent, hence it is not the polymyositis alone which causes it. In one case of this type which I recently observed, and in which trichinosis was definitely excluded, there was no eosinophilia, and in three cases reported by Benjamin T. Burley[1] he had the same experience. On the other hand, if the hypothesis be correct that a specific toxin caused by the agency of the parasite is responsible for the aggregation of eosinophiles, which occurs around the organisms in between the muscle fibers, one would naturally expect the eosinophilia of the blood to be at its maximum before the parasites became encysted and quiescent; yet in many of the cases herein recorded, such was not the fact, notably in that of the patient whose maximum eosinophilia of 62 per cent. was not reached until more than six weeks after his first symptoms appeared, when he was practically well. It is difficult to understand how in such a case the eosinophilic response can be in any sense protective. Moreover, the eosinophilia is entirely independent of definite relationship to either the general leukocytosis or course of the fever. The question is obscure and experimental evidence is much needed to elucidate it. Some of the tapeworms, notably the dibothriocephalus latus, are known to generate specific

[1] Jour. Amer. Med. Assoc., January 18, 1908.

toxins causing anemia, yet their eosinophilic response is much less than that of trichinosis. In a case of this sort which I have elsewhere reported,[1] the eosinophilia never exceeded 9 per cent., although a condition of pernicious anemia was produced of extraordinary degree.

Von Leube[2] states that it is impossible to distinguish polymyositis from trichinosis in many cases without examination of excised muscle, and Hepp[3] in an early account of polymyositis referred to it as "Pseudo-trichinose," but in the light of recent study the diagnosis ought not to be so difficult even without excision of muscle, for in polymyositis eosinophilia is lacking, as well as the eye pains, marked headache, puffiness of the eyelids, vomiting and peculiar dyspnea which characterize all the more severe cases of trichinosis. Apart from polymyositis, those diseases for which trichinosis is most often mistaken are typhoid fever, paratyphoid fever, septicemia, acute rheumatic fever, estivo-autumnal fever, multiple neuritis, and acute poliomyelitis.

The temperature charts of cases of trichinosis very often closely resemble typical charts of typhoid fever in the third and fourth week, and the headache and occasional epistaxis may be confusing, but in trichinosis the patient is usually proportionately less ill and lacks the nervous phenomena of typhoid fever.

Moreover, the onset of trichinosis is more acute, with vomiting and muscular pains and cramps. The two diseases may, however, co-exist, as they did in the original case of Zenker, which led him to discover the trichinæ in a routine examination for degenerated muscle fibers in a patient who had died from typhoid fever.

Fischer[4] and McCrae[5] have each reported a case of combined trichinosis and typhoid infection.

Exceptionally the trichinosis charts may resemble the markedly remittent temperature curve of septicemia or of a estivo-autumnal fever with chills and sweats, but a thorough examination of the blood in all such cases ought to resolve all doubt.

Occasionally in trichinosis there is swelling about such major joints as the knees and ankles, and this with the pain caused by

[1] Med. News, April 8, 1905.
[2] Medical Diagnosis.
[3] Berl. klin. Woch., 1887, xxiv, 297–322.
[4] Deut. med. Woch., 1898, xxiv, 821.
[5] Amer. Jour. Med. Sci., 1902, cxxiv, 56.

voluntary movement and sweating may give rise to an erroneous diagnosis of rheumatism. I have lately seen a case which had been mistaken for rheumatism for a week, owing to such symptoms and the fact that the patient a year before had had a typical acute articular rheumatism. The hemorrhages into the cornea led me to suspect the presence of trichinosis, and the latter diagnosis was confirmed by finding eosinophilia and the presence of trichina in an excised fragment of the gastrocnemius.

I saw another interesting case in a lad, aged eighteen years, in which a diagnosis of rheumatism similarly had first been made, for which that of acute poliomyelitis had later been substituted by the physicians in attendance.

The latter diagnosis was held because of a recent epidemic of poliomyelitis occurring in the same locality, and the patient suffered such excruciating pains in the extremities that lack of motion was mistaken for paralysis. Having demonstrated that paralysis did not exist, I suspected trichinosis from the slight puffiness of the eyelids and a diaphragmatic type of dyspnea. I obtained a blood examination as follows:

Hemoglobin	85 per cent.	
Erythrocytes	5,032,000	
Leukocytes	24,300	
Polynuclear cells		76.5
Transitional		0.9
Lymphocytes		7.4
Eosinophiles		15.2
		100.0

I found that the patient had eaten poorly cooked "Bolognas" two weeks prior to his illness, and a similar milder case was found in the cook who had partaken of the same food.

To recapitulate, there should be no difficulty in determining promptly a correct diagnosis of trichinosis based upon the observation of the following symptoms:

1. Acute onset, usually with vomiting and abdominal cramps.
2. A high grade of eosinophilia invariably present.; usually above 30 and frequently much higher, even above 80 per cent.
3. A high grade of temperature, often reaching 104 or more and lasting in lessening degree for two to six weeks.

4. Puffiness of the eyelids and face, with pains in the eyes occurring in one-fourth of the cases.

5. Dyspnea and diaphragmatic breathing occurring without cyanosis in about one-fourth of the cases.

6. The generalized muscle pains, cramps, soreness, and prostration, causing sometimes deceptive apparent immobility.

7. The sudden occurrence of symmetrical circumscribed corneal hemorrhages in a patient whose bloodvessels are not degenerate, should give rise to a suspicion of trichinosis.

DISCUSSION.

Dr. Richard C. Cabot: With regard to the edema, that of the eyes and hands is common. In the past year at the Massachusetts General Hospital we have had one case with general anasarca and dropsy of all the serous cavities. This case was remarkable in another respect; we recovered the trichinæ from the muscles, yet there was no eosinophilia during the first ten days; at the end of the tenth day the eosinophiles rose and remained high for a number of weeks. In another case, the patient was entirely free from pain. In a third case we recovered embryos from the blood by the method described by Dr. Janeway.

FREQUENCY AND SIGNIFICANCE OF ALBUMIN IN THE URINES OF NORMAL CHILDREN.

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For some years past we have been much impressed by the frequency with which albumin, varying in amounts from very slight to marked traces, has been reported present in the urines of children we have seen in private practice. In these children we have been unable to detect abnormalities which we considered sufficient to account for the albumin.

Stimulated by these findings, we undertook the studies set forth in this paper, and in presenting them we shall not undertake a discussion of the extensive and valuable work which has been done on the albuminurias, but merely state the results of our own work. Our purpose has been to determine the frequency of occurrence of albuminuria, and, if possible, to throw some light upon the cause of this frequency. To this end we have made examinations of the urines of 124 presumably normal children, taking samples at frequent intervals on the same day, and over a period of days, as well as samples covering the full twenty-four-hour period.

In carrying out this work, we have considered it advisable to make complete examinations of the urine and to use tests easy of application and at the same time reliable.

The following is an outline of our routine procedure: In each sample of urine we determined the color, the appearance, the specific gravity, the reaction (in twenty-four-hour specimens the total acidity), the presence or absence of albumin, sugar, acetone, diacetic

acid, indican, urobilinogen, and phenol; and microscopically, the presence or absence of cells, casts, cylindroids, and crystals.

Tests Used. For the determination of the specific gravity we used Squibb's urinometer, graduated to 25° C.; for the reaction, litmus paper; for albumin (all specimens having been made clear either by filtering or by the addition of magnesia and filtration), Heller's nitric acid test, observed at intervals of one, three, and five minutes; the heat test, observing it immediately as well as after the addition of acetic acid; the potassium ferrocyanide test, contrasting it with the cold urine to which acetic acid had been added; and the acetic acid test, in which a few drops of 50 per cent. acetic acid were added to the untreated urine. In each of these tests, in addition to the contrasts made above, comparisons were made with the untreated urine and always against a black background. When the specific gravity was 1024 or over, the urine was diluted and both samples tested. For sugar, we used Fehling's test; for acetone, Lange's test, controlled by Stock's test; for diacetic acid, Gerhardt's test; for indican, Obermayer's test; for urobilinogen, the dimethylamidobenzaldehyde reaction; and for phenol, the urine was treated with 25 per cent. sulphuric acid and the distillate with bromine water. In the microscopic examination, two slides from the centrifugated sediment were studied.

The routine examination for bodies other than albumin was made in order to determine whether, if present, they might have some bearing upon the occurrence of the albumin, or indicate some abnormal condition to which it could be attributed.

With the same idea in view, we examined the stools in certain groups of cases, amounting to about one-third the total number. This included the form, color, odor, reaction, and evidences of fermentation and the presence of mucus and undigested food particles; and under the microscope the presence of starch, neutral fats, soaps, and crystals.

Source of Material. Four hundred and forty-five specimens of urine were examined. These were obtained from 124 children, ranging in age from eighteen months to fourteen years. For convenience of consideration, we have divided these latter into four groups, as follows:

I. Children obtained from a number of different sources.

II. Children obtained from the Orthopedic Ward of the Hospital of the University of Pennsylvania, suffering from congenital or acquired deformities (other than tuberculous).

III. Children from the Baptist Orphanage of Philadelphia.

IV. A group of three children, whose urines were examined practically every day for several weeks.

Specimens Used. In the majority of the children in Group I, only morning samples were examined; in a smaller number, both morning and evening.

In Group II, consisting of 31 cases, only morning examinations were made in 19; both morning and evening, in 18; and morning, noon, and evening for two successive days, in 3 cases. In the last case of this group, for reasons to be considered later, examinations were made for six successive days. The first sample was taken immediately upon waking, the second at 9 a.m., and the others at noon and evening. On the first day the child was up and about the ward, and on the regular hospital diet; on the second day he was in bed, on the same diet; on the third day the conditions were the same; on the fourth day he was again up and about, on the hospital diet; on the fifth day he was up and about, on an exclusive milk diet; on the sixth day he was in bed, on a milk diet.

Group III consisted of 36 institutional children. We are quite aware that the normality of such children may be questioned, but they are included because, aside from being well nourished and free of organic diseases, the conditions under which they live are entirely normal. The Home is constructed on the cottage plan, each cottage being under the direction of a house mother, who has charge of about 25 children. The food supplied them is not only adequate, digestible, and well balanced, but also admirably prepared. The sleeping apartments are spacious, well ventilated, and perfectly clean. The playground consists of an enclosure of about six acres. Aside from this the children are still further detached from the ordinary institutional environment by the fact that they receive their education in the public schools.

During the period of examination the usual routine of life was followed, except that the children were kept from school. They

were studied in groups of 3, each group being under the constant supervision of a trained nurse, in order to insure the proper collection of specimens. The following routine was then adopted: A complete physical examination was made, to exclude acute and chronic diseases and defects of development. The specimens were collected immediately upon rising, and thereafter at 9 A.M., 12 noon, and 6 P.M. In addition, the total quantity for twenty-four hours was taken. The body temperatures were recorded every fourth hour during the day. The pulse rate and the blood pressure (Stanton's apparatus) were determined in the upright and recumbent postures on the day that the samples were collected, and a sample of the stools from each case was taken.

In Group IV 95 examinations were made. The specimens represented the morning urine for a portion of the time, the mid-day for another, and both the morning and evening for the balance. On two occasions, separated by some days, the twenty-four-hour quantity was collected and examined.

Results of the Examinations. There has been wide variation in the specific gravity of the urine voided at different periods of the same day. In the majority it has been higher in that voided immediately upon rising and in the urine voided at the end of the day, but this has not been constant. In the twenty-four-hour specimens (42 in number) the specific gravity has been much higher than the averages given in text-books and monographs for children whose ages were the same as those we have studied. The specific gravity bore no definite relationship to the amount of urine voided. Thus, in a child voiding but 475 c.c. in twenty-four hours, the specific gravity was 1022, while in another, voiding 1250 c.c.—one of the largest amounts recorded—the specific gravity was 1025. Neither the form nor the amount of albumin present bore any relationship whatsoever to the variations in the specific gravity or to the amounts voided.

Variations in the reaction had no influence upon the albuminuria. In one of the cases in Group IV (the 3 cases from whom samples were examined daily over a period of weeks) we noted a rather interesting condition, from which, however, no conclusions can be drawn. An evening sample of one day had a specific gravity of 1030; it was

markedly acid, contained a very slight trace of nucleo-albumin, and the sediment showed amorphous urates. The urine of the following morning showed a marked turbidity when voided, which was due to a fine white flocculent precipitate; its reaction was strongly alkaline; it contained no albumin, but showed an abundant precipitation of phosphates on boiling, and the sediment contained large quantities of earthy phosphates. A sample voided in the early afternoon of the same day had a specific gravity of 1028; its reaction was strongly acid and it contained a very slight trace of nucleo-albumin, the sediment showing amorphous urates and calcium oxalate crystals.

One cannot argue that the absence of albumin in the second sample was dependent upon the alkaline reaction, since albumin was absent in this boy's samples not infrequently when the urine was strongly acid. But the high phosphatic content of the morning urine, wedged in between samples which were highly acid, is interesting and difficult of explanation. Its interest is greatly increased, moreover, by the fact that this is a common and not unique occurrence in the experience of this boy. On one other occasion, noted in our tables, morning samples on two successive days showed in the one a highly acid urine with nucleo-albumin, and in the next a highly alkaline urine without albumin. On several occasions, not recorded in our tables, we have observed this boy pass a highly alkaline urine on rising, and within a few hours void a urine which was definitely or strongly acid. We desire to emphasize the fact that the phosphates were present only in the morning samples, and therefore not dependent upon the diet.

In none of the cases examined have we found sugar, acteone, or diacetic acid, and those substances may be eliminated as having any bearing upon the occurrence of the type of albuminuria under discussion.

In 254 examinations, indican was present twenty times, phenol thirty-seven times, and urobilinogen twenty-one times. While albumin was associated with these bodies in the majority of instances, it was sometimes absent when they were all present, and the amount was never greater when associated with them than it was in the specimens in which they were absent. To state the

results in fuller detail, indican was present three times without albumin, and in association with phenol and without albumin five times, and once with both phenol and urobilinogen in the absence of albumin. Phenol alone was present without albumin five times.

Turning now to the possible influences of the substances demonstrable by the microscope, we would state that in no instance were epithelial cells or leukocytes present in excess of the normal. In one case, in two specimens collected on successive days, a few erythrocytes were noted, but they were not associated with casts or cylindroids. In the first of these, an evening specimen, there was present a very slight trace of nucleo-albumin, and in the second, a morning specimen, both serum and nucleo-albumin were present in very slight traces.

In considering the relationship of crystals to the presence of albumin, it is necessary to bear in mind the possibility that in some instances they may have been precipitated out after the urine had been voided. This is especially likely to have occurred, because we have depended entirely upon low temperatures for the preservation of the specimens.

In the 248 sediment examinations uric acid crystals were found alone fifty-one times. In these samples albumin was entirely absent five times. Serum albumin was present alone in slight traces twice, and nucleo-albumin alone either in slight or very slight traces thirty-five times. In nine instances, both forms were present as traces, slight traces, or very slight traces. In 7 of these samples, occasional casts and cylindroids were found.

Calcium oxalate crystals were present alone in 38 samples; 12 of these had no albumin, 2 had serum albumin alone in very slight traces, 18 had nucleo-albumin alone in amounts varying from traces to very slight traces. In the 6 remaining cases both varieties were found in correspondingly small quantities; casts were not found in any of the samples.

Ammonium urates were present alone three times, and amorphous urates ten times, and in twenty-two instances they were both present. The findings as to albumin were practically the same as in the case of the uric acid and calcium oxalate crystals.

In the samples containing uric acid crystals alone, casts were

noted rather more often than in the samples showing the other forms of crystals, but there was no increase in the amount of albumin as compared with other specimens, nor in the amount of cellular elements. That these findings as to casts in the samples, showing uric acid crystals alone, is probably accidental is borne out by the fact that in 13 samples showing both uric acid and calcium oxalate crystals occasional hyaline casts were present but once.

We do not find any evidence, therefore, to indicate that crystals, when present in amounts such as are found in the average normal child are in any way responsible for the associated albumin. In the children in Group IV, whose urines were examined over a period of weeks, we have several times found uric acid crystals present without albumin. The same can be said of the various other crystals, and it is also true that the amounts of albumin varied in the same way when associated with crystals as when present without them.

The stools were examined seventy times in 69 different children. In 50 children they were normal; in the 19 remaining, there were moderate variations from the normal, such as offensive odor, abnormal consistence, undigested food particles, starch granules, and fat. The results of the examinations for albumin in the urines of these two groups showed absolutely no difference as to the frequency of occurrence, the quantity eliminated, or the form of the albumin. Thus in one instance in the latter group, albumin was absent when the stool was unformed, malodorous, soft and mushy, with slight fermentation, and showing starch granules microscopically. Therefore, we conclude that these mild disturbances of the intestinal digestion in apparently normal children, discoverable only by examination of the stools, are not sufficient to account for the occurrence of the albumin. This conclusion is fully confirmed by our findings in severe cases of intestinal indigestion, which sometimes show no albumin and rarely give more marked reactions for albumin than those we have noted in these presumably normal children.

Complete physical examinations were made in all the cases except those comprising Group II. In these, evidences of disease were eliminated by the hospital records. In our own examinations we gave special attention to the cardiovascular system, in order to

eliminate valvular and myocardial changes, degenerations of the vessels, and variations in the arterial tension. We found murmurs of a functional nature very common, but in no way related to the presence of albumin. All cases with evidences of organic disease of which we met several in the course of our studies, were excluded. In Group III we made systematic studies of the blood pressure in both the upright and recumbent postures. The systolic pressure varied in these 36 cases from 85 to 119, the average being about 100. The difference in pressure between the upright and the recumbent was insignificant—about 5 mm. on the average. The figures 85 to 119 are probably within the normal range of variation, if one considers the nervous influences which were active in consequence of the examinations. In some children the effect of these influences was to increase the arterial tension, while in others the pressure was lowered. In several instances the pressure, which was primarily low or high, rapidly returned to the normal after the child had become accustomed to the examination. In any event, the urinary findings as to albumin were the same in the high and the low pressures, and in neither were they different from the findings in those cases with blood pressures at or near 100.

The great majority of the children whose urines we have studied have been on mixed and varied diets. In three instances, however, in which we were able to control the children, we have studied the urine while they were on their ordinary diets, and again while they were on exclusive milk diets.

In the first case two examinations were made, at intervals of two days, while the child was on a mixed diet. In the first sample examined there was present a trace of both serum and nucleo-albumin, and in the second a very slight trace of nucleo-albumin. After the child had been on an exclusive milk diet for one week, another specimen was examined, which contained a trace of both serum and nucleo-albumin. An examination made two days later showed slight traces of each.

In the second case an examination made while the child was on a mixed diet showed a very slight trace of nucleo-albumin. A second examination, made after the child had been on an exclusive milk diet for two days, gave the same result, as did also the third

examination, which was made after the milk diet had been continued for twelve days.

The third case is the one previously referred to under Group II, in which the urine was examined for six successive days. On the first day, while the child was on a mixed diet, one examination was made, which showed no albumin. On the second day, four specimens were examined—the first showed no albumin; the second, a very slight trace of nucleo-albumin; the third, a slight trace of both albumins; and the fourth, a very slight trace of nucleo-albumin.

On the third day, while still on a mixd diet, four examinations were made. The first showed a very slight trace of nucleo-albumin; the second and third, slight traces of nucleo-albumin; and the fourth, a very slight trace of serum albumin.

On the fourth day, the mixed diet being continued, the results of three examinations showed: in the first, a very slight trace of nucleo-albumin; in the second, no albumin; and in the third, a very slight trace of nucleo-albumin.

On the fifth day, while on a milk diet, four examinations showed: in the first, a very slight trace of nucleo-albumin; in the second and third, slight traces; and in the fourth, no albumin.

On the sixth day, the milk diet being continued, the first of three examinations showed a very slight trace of nucleo-albumin, and the others no albumin.

These few results are, of course, in no sense conclusive, but in so far as they go they suggest that there is no difference in the albumin elimination on the two kinds of diet described. One might infer that in Case III the results did indicate a difference, were it not that this same child, on several previous occasions, had shown no albumin in his urine when on a mixed diet. This case, however, illustrates well a common characteristic of these albuminurias, which it may be well to emphasize here, and that is, their marked variability. Different samples on the same day showed sometimes no albumin, and again nucleo-albumin, and at other times, first, nucleo-albumin, and later, serum albumin.

Throughout our studies we have borne in mind the relationship of posture to the elimination of albumin. In no instance have we obtained evidence which we consider sufficient to justify us in

classifying any of our cases under the heading of postural or orthostatic albuminuria. In 49 children, however, we have endeavored to exclude the factor of position by having them void urine immediately upon waking; 36 of these (Group III) were studied successively in groups of 3. These children slept in a room with a trained nurse. No mechanical means were used to restrain them, but they were under the close supervision of a conscientious and interested observer, and in so far as she could determine, they neither sat up in bed nor were out of bed during the night. At 6 A.M. they were awakened and required to void urine immediately. The remaining 13 (Group II) were treated in the same manner by the night nurse on duty, but as her requirements occasionally took her from the ward, it is reasonable to assume that they were less well controlled.

In 2 children in the group of 36 we considered the possibility of this relationship mainly because of the amount of albumin sometimes noted, which, at its highest, was recorded as a marked trace of both serum and nucleo-albumin. For this reason, in addition to the specimen voided on rising, we studied two samples voided after periods of rest during the day. The bladders were emptied and the children at once placed in the recumbent posture, where they were kept until they desired to void urine again. On one occasion the specimens voided after the night's rest, as well as those voided after the day's rest, showed less albumin than at some other hours of the day, but it was, nevertheless, present. The morning urine in one showed only slight, and in the other very slight, traces of nucleo-albumin. On the other hand, one of these boys voided a sample at 9 A.M. which contained no albumin, and neither of them showed a decrease in the amount of albumin at the end of the day, one of them, in fact, showing marked traces in the evening. Throughout the day the amounts varied markedly. In other words, in neither of these cases did the findings correspond to the accepted requirements for this form of albuminuria.

Owing to the fact that albumin was occasionally present in marked traces in these two cases, and because one of them showed a very few casts and cylindroids, it would seem almost more difficult to eliminate the possibility of nephritis than to eliminate the ortho-

static form of albuminuria. As against this view, we would point out that in one of these cases albumin was absent on one occasion, and in both the amount of albumin fluctuated from hour to hour, varying from a very slight to a marked trace. Furthermore, there was nothing in the condition of the children to suggest a lesion of the kidneys. Both were unusually well nourished, their color was good, they had no symptoms of ill health, and their cardiovascular conditions showed nothing abnormal.

The study of the presence of casts and cylindroids in these groups of cases shows that 28 children, or 22.5 per cent., had occasional hyaline casts associated with cylindroids, and 6 had cylindroids without casts. In some of them more than one specimen showed these formed elements. Taking the total number of specimens (amounting to 40), we find that casts and cylindroids were associated thirty-three times, and cylindroids were present alone seven times. The relationship of these formed elements to albumin was as follows: Of the 33 specimens showing both casts and cylindroids, 1 showed no albumin; 26, very slight traces of nucleo-albumin; 2, a slight trace; 1, a trace; 2 others, a very slight trace of serum albumin; and 1, a very slight trace of both serum and nucleo-albumin. Of the 7 specimens showing cylindroids alone, 2 showed no albumin; 3, a very slight trace of nucleo-albumin; and 2, very slight traces of both serum and nucleo-albumin.

Many of the older writers contend that the occurrence of casts and cylindroids in the urine is an indication of a permanent impairment of renal function The views of recent writers, however, have been more liberal. Jehle makes the statement that "the occurrence of casts, erythrocytes, and various epithelial cells is not necessarily a criterion of nephritis, since they are found in the urine of lordotics." Fischl supports this view and is especially impressed by it, since it fully confirms results which he obtained in animal experimentations —by suspending rabbits, as well as by producing in them an artificial lordosis, he was able to demonstrate the above-mentioned elements in the urine. One of the animals which he killed showed no microscopic changes in the kidneys other than congestion, and three of the others in this series, after being released for a period of time, voided entirely normal urine.

We are inclined to believe that these elements as we have found them are merely products of a temporarily overtaxed kidney, resulting from variations in the habits of life of the individual, which are so slight as to be difficult of recognition.

We now come to a consideration of the albumins. In the urines of 124 children we found albumin at some time in 110, or in 88.7 per cent. Albumin was present in two forms—(1) serum albumin, and (2) an albuminous body, which was precipitated by acetic acid in the cold. For purposes of convenience, but with a full appreciation of the unsettled state of our knowledge regarding the nature of this latter body, we have used for its description the term nucleo-albumin.

The proportions of the different albumins present in these 124 children were as follows: 34, or 27.4 per cent., showed serum albumin—alone (4) and in combination (30); and 106, or 85.4 per cent., nucleo-albumin—alone (76) and in combination (30). In other words, this so-called nucleo-albumin was present three times as often as serum albumin.

We are convinced that these figures do not fairly represent the frequency of occurrence of either of these albumins. This statement is based upon the following facts: In Group I there were 33 children from whom we examined but one sample; in this number nucleo-albumin was present twenty-five times, equalling 75.8 per cent., as compared with 85.4 per cent. for the total number of children, and 94.7 per cent. for 38 children from whom we made examinations of the twenty-four-hour quantity.

In this same group of 33 children serum albumin was present seven times, which was equal to 21.2 per cent., as compared with 27.4 per cent. for the total number, and 42.1 per cent. for the 38 children from whom we made examinations of the twenty-four-hour quantity.

We are inclined to believe that had we examined not only the twenty-four-hour quantities but also a number of samples voided at different hours of the day, and continued these examinations over a period of days, we might have been able not only to demonstrate the presence of nucleo-albumin at some period in the urine of every child examined, but also to have increased the percentage of

cases showing serum albumin. In the one child in whom we failed to find either form of albumin in the twenty-four-hour specimen (a child in Group IV), nucleo-albumin was frequently found in the daily examinations, and serum albumin occasionally.

Believing, therefore, that it is possible to demonstrate in the urine of every presumably healthy child traces of an albuminous body precipitated by acetic acid, we are naturally forced to the conclusion that its presence cannot necessarily be considered an indication of a lesion of the kidneys, and that it must, therefore, be regarded as an exceedingly common, if not constant, manifestation in the urines of children under fourteen years of age, and that it is consequently of no clinical significance.

As to the interpretation of the serum albumin, we believe that the cause suggested for the occasional presence of casts and cylindroids is quite sufficient to account for its occurrence in the amounts in which it has been present in the urines we have examined, for it must be borne in mind that in all of our cases neither the nucleo nor serum albumins have ever been present in more than traces, and in the vast majority only in very slight traces.

Summary. 1. There has been no relationship between the specific gravity and the form or amount of albumin.

2. The reaction has had no influence upon the production of albumin.

3. Sugar, acetone, and diacetic acid were never found. They may, therefore, be considered as having no bearing upon the production of albumin.

4. Indican, phenol, and urobilinogen, when present, were usually associated with albumin, but albumin was sometimes absent when they were all present, and the amount was never greater when associated with them than it was in the cases in which they were absent.

5. Crystals, when present in amounts, such as are occasionally found in normal children, are in no way responsible for the associated albumin.

6. The mild disturbances of the intestinal digestion, as shown by the examination of the stools, were not sufficient to account for the occurrence of albumin.

7. The blood pressure was within the normal range in all cases, and, therefore, did not influence the albumin output.

8. The albumin elimination was the same on mixed and exclusive milk diets.

9. We found no children in whom the albumin excretion corresponded to the requirements for postural or orthostatic albuminuria —a rather surprising result in view of the frequency with which this condition is supposed to occur.

10. 22.5 per cent. of the children showed occasional hyaline casts and cylindroids in their urines. We do not consider their "occasional presence" as indicative of a lesion of the kidneys, but rather as suggesting a temporary overtaxation of the kidneys, resulting from variations in the habits of life of the individuals which are too slight to be recognized.

11. 88.7 per cent. of the urine of these 124 children showed albumin, 27.4 per cent. showing serum albumin alone and in combination, and 85.4 per cent. an albuminous body precipitated by acetic acid in the cold, either alone or in combination. These two albumins were nearly always present in *very slight traces*, occasionally in *slight traces*, and rarely in *traces*.

In 38 children, the twenty-four-hour specimens showed nucleo-albumin in all but one, and in this case samples examined over prolonged periods of time showed nucleo-albumin frequently.

In these 38 children the percentage of serum albumin was very much higher (42.1 per cent.) than in the total number of cases examined. We believe, therefore, that it is possible to demonstrate in the urine of every presumably healthy child traces of an albuminous body precipitated by acetic acid. Consequently, this substance must be regarded as an exceedingly common, if not constant, manifestation in the urine of children under fourteen years of age, and as of no clinical significance.

We do not believe that serum albumin in the amounts in which it appears in these children indicates a diseased condition of the kidneys any more than does the presence of occasional hyaline casts and cylindroids, and that its etiology may be considered the same as that given for these formed elements.

GROUP I.—*Children Obtained from a Number of Different Sources.*

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
J. G.	6 years	A.M. 12- 7-09	L. amber acid	1010	S. t. nucleo	None	Urobilinogen Phenol	None
M. J. (f)	3 years	A.M. 1-22-10	L. amber acid	1018	V. s. t. nucleo	None	None	Hyaline Cylindroid
J. C.	10 years	A.M. 1-24-10	Amber acid	1021	V. s. t. nucleo	None	Phenol	Hyaline Cylindroid
Y. K. (f)	6 years	A.M. 1-19-10	L. amber acid	1018	None	None	Phenol	Uric acid
P.	7 years	A.M. 1-28-10	Amber acid	1016	V. s. t. nucleo	None	None	None
M. E. (f)	12 years	A.M. 2-20-10	L. amber acid	1021	V. s. t. nucleo	None	None	None
J. B.	7 years	A.M. 11-29-09	L. amber acid	1010	V. s. t. nucleo	None	None	Cylindroid
H. L.	6 years	A.M. 11-23-09	Amber acid	1030	S. t. nucleo	None	Phenol	Amorp. urates
J. L.	18 mos.	A.M. 11-15-09	L. amber acid	1022	S. t. serum	None	Urobilinogen	Cal. oxalate Amm. urates
S. R. (f)	10 years	A.M. 12- 4-09	L. amber acid	1020	V. s. t. nucleo	None	None	None
H. C. (f)	10 years	A.M. 1-22-10	Amber acid	1018	T. serum T. nucleo	None	None	None
R. W. (f)	6 years	A.M. 11-29-09	L. amber acid	1020	V. s. t. nucleo	None	Phenol	Cal. oxalate
H. Clark	4 years	A.M. 11-29-09	L. amber acid	1020	V. s. t. nucleo	None	None	None
C. W.	8 years	A.M. 11-29-09	Pale acid	1018	None	None	Urobilinogen Phenol	None
S. W. (f)	12 years	A.M. 11-29-09	Pale acid	1015	V. s. t. nucleo	None	Phenol	Amorp. urates
S. R. (f)	3 years	A.M. 11-23-09	L. amber acid	1027	V. s. t. nucleo	None	None	None
L. McC (f)	11 years	A.M. 11- 9-09	L. amber acid	1022	V. s. t. nucleo	None	Indican Phenol	None
A. H.	8 years	A.M. 11-10-09	L. amber acid	1016	V. s. t. nucleo	None	None	None
E. B. (f)	10 years	A.M. 11- 3-09	Amber acid	1026	S. t. nucleo T. serum	None	Urobilinogen	None
E. W. (f)	6 years	A.M. 12-17-09	L. amber acid	1029	V. s. t. nucleo	None	None	Hyaline Cylindroid
T. C.	6 years	A.M. 11- 8-09	Pale acid	1008	V. s. t. nucleo	None	None	None
T. C.	6 years	A.M. 11-11-09	L. amber acid	1016	None	None	Indican Urobilinogen	None
H. T. (f)	14 years	A.M. 2-10-10	L. amber acid	1020	V. s. t. nucleo S. t. serum	None	Phenol Urobilinogen	Cal. oxalate
M. S. (f)	10 years	A.M. 2-10-10	Amber acid	1020	T. nucleo	None	None	Uric acid
E. H.	2 years	A.M. 3-11-10	Amber acid	1030	S. t. nucleo	None	None	Hyaline Cylindroid
R. Z.	9 years	A.M. 3-11-10	L. amber acid	1027	S. t. nucleo	None	Urobilinogen	Cal. oxalate Cal. oxalate
E. W. (f)	6 years	A.M. 3- 2-10	L. amber acid	1026	None	None	None	None
F. F.	6 years	A.M. 3-11-10	L. amber acid	1020	V. s. t. nucleo	None	None	Hyaline Cylindroid
L. S. (f)	9 years	A.M. 3-11-10	L. amber acid	1020	V. s. t. nucleo	None	None	Uric acid
T. C.	2 years	A.M. 12- 8-09	Amber acid	1030	None	None	None	None
S.	5 years	A.M. 12-10-09	L. amber acid	1010	V. s. t. nucleo	None	Indican Phenol	None
W. G.	9 years	A.M. 12-10-09	L. amber acid	1010	V. s. t. nucleo	None	None	None
L. B. (f)	9 years	A.M. 12-10-09	Amber acid	1013	None	None	None	Hyaline Cylindroid
E. C. (f)	14 years	A.M. 12-20-09	Amber acid	1014	None	None	None	Uric acid

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
R. C. (f)	4 years	A M. 12–20–09	L. amber acid	1015	V. s. t. nucleo	None	Phenol	None
R. W. (f)	7 years	A.M. 12–20–09	Amber acid	1027	None	None	None	None
M. C. (f)	10 years	A.M. 12–20–09	L. amber acid	1022	S. t. nucleo S. t. serum	None	None	Amorp. urates
J. S. (f)	18 mos.	A.M. 12–30–09	L. amber acid	1024	None	None	Urobilinogen	None
B. S. (f)	18 mos.	A.M. 11–26–09	L. amber acid	1022	V. s. t. nucleo	None	None	Cal. oxalate
B. S. (f)	18 mos.	A.M. 11–29–09	Amber acid	1020	V. s. t. nucleo	None	None	None
B. S. (f)	18 mos.	A.M 12– 2–09	Pale acid	1022	V. s. t. nucleo	None	None	None
B. S. (f)	18 mos.	A.M. 2–10–10	L. amber acid	1024	V. s. t. nucleo	None	None	None
B. S. (f)	18 mos.	A.M. 2–14–10	L. amber acid	1017	V. s. t. nucleo	None	None	None
J. K. (f)	10 years	A.M. 11– 3–09	L. amber acid	1018	V. s. t. nucleo V. s. t. serum	None	None	Cal. oxalate
J. K. (f)	10 years	A.M. 11–16–09	L. amber acid	1016	V. s. t. nucleo V. s. t. serum	None	Indican Phenol	None
J. K. (f)	10 years	A.M. 12–20–09	L amber acid	1024	V. s. t. nucleo	None	Urobilinogen	Cal. oxalate
J. K. (f)	10 years	A.M. 2– 6–10	L. amber acid	1026	V. s. t. nucleo	None	None	Hyaline Cylindroid
A. R. (f)	8 years M'xd diet	A.M. 1–19–10	L. amber acid	1020	T. nucleo T. serum	None	None	Hyaline Cylindroid
A. R. (f)	8 years Milk diet	A.M. 1–21–10	L. amber acid	1021	V. s. t. nucleo	None	Phenol	None
A R. (f)	8 years Milk diet	A.M. 1–28–10	Amber acid	1020	T. nucleo T. serum	None	Urobilinogen	None
A. R. (f)	8 years Milk diet	A.M. 2– 3–10	L. amber acid	1016	S. t. nucleo S. t. serum	None	Phenol	None
A. R. (f)	8 years	A.M. 2– 4–10	L. amber acid	1020	V. s. t. nucleo	None	Phenol	None
J. B. (f)	10 years(f)	A.M. 3–11–10	L. amber acid	1021	V. s. t. nucleo	None	Indican Phenol	Uric acid
J. B. (f)	10 years(f)	A.M. 3–15–10	L. amber acid	1024	V. s. t. nucleo	None	None	None
J. L.	6 years	A.M. 1–19–10	L. amber acid	1026	None	None	Phenol	None
J. L.	6 years	A.M. 1–24–10	L. amber acid	1020	V. s. t. nucleo	None	Indican Phenol	Hyaline Cylindroid
J. L.	6 years	A.M. 1–22–10	L. amber acid	1020	None	None	None	None
J. L.	6 years	A.M. 1–25–10	L. amber acid	1016	None	None	Phenol	None
R. N. (f)	11 years	A.M. 1–19–10	L. amber acid	1017	None	None	None	None
R. N (f)	11 years	A.M. 1– 3–10	L. amber acid	1020	T. nucleo	None	Urobilinogen Phenol	None
R. N. (f)	11 years	A.M. 1–10–10	L. amber acid	1018	V. s. t. nucleo	None	None	Cal. oxalate
E. H.	6 years M'xd diet	A.M. 2–18–10	L. amber acid	1018	V. s. t. nucleo	None	None	None
E. H.	6 years Milk diet	A.M. 2–20–10	L. amber acid	1020	V. s. t. nucleo	None	Urobilinogen	None
E. H.	6 years	A.M. 2–27–10	L. amber acid	1018	V. s. t. nucleo	None	None	Cal. oxalate
B. M.	6 years	A.M. 1–30–10	Amber acid	1020	V. s. t. nucleo	None	Indican	None
B. M.	6 years	A.M. 1–31–10	L. amber acid	1018	V. s. t. nucleo	None	None	Uric acid
M. C. (f)	10 years	A.M. 2– 2–10	L. amber acid	1028	S. t. nucleo	None	Phenol	Cal. oxalate
M. C. (f)	10 years	A.M. 2–22–10	L. amber acid	1018	S. t. nucleo	None	None	None
J. C.	11 years	A.M. 11–15–09	Amber acid	1030	S. t. nucleo S. t. serum	None	None	Hyaline Cylindroid
J. C.	11 years	A.M. 11–18–09	L. amber acid	1020	V. s. t. nucleo	None	Urobilinogen Phenol	Cal. oxalate

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
J. C.	11 years	A.M. 11–22–09	L. amber acid	1020	V. s. t. nucleo V. s. t. serum	None	Phenol	None
F. C.	14 years	A.M. 11–15–09	L. amber acid	1022	S. t. nucleo	None	None	None
F. C.	14 years	A.M. 11–22–09	Amber acid	1023	V. s. t. nucleo	None	Phenol	None
F. C.	14 years	A.M. 11–18–09	L. amber acid	1020	V. s. t. nucleo	None	Urobilinogen Phenol	Cal. oxalate
K. K.	12 years	M. 11–26–09	Amber acid	1020	None	None	None	None
K. K.	12 years	A.M. 11–27–09	L. amber acid	1026	V. s. t. nucleo	None	None	None
J. H. (f)	5 years	A.M. 11–25–09	L. amber acid	1017	V. s. t. nucleo	None	Phenol	Amorp. urates
J. H. (f)	5 years	A.M. 11–27–09	L. amber acid	1020	S. t. nucleo	None	Urobilinogen	None
F. K.	8 years	A.M. 12– 4–09	L. amber acid	1022	V. s. t. nucleo	None	Phenol	None
F. K.	8 years	A.M. 12– 8–09	Pale acid	1025	V. s. t. nucleo	None	None	None
F. K.	8 years	A M. 12– 9–10	L. amber acid	1020	V. s. t. nucleo	None	None	None
P. W.	2 years	A.M. 12–22–10	L. amber acid	1016	V. s. t. nucleo	None	None	None
P. W.	2 years	P.M. 12–22–10	Amber acid	1020	V. s. t. nucleo	None	None	Cal. oxalate
J. W.	4 years	A.M. 12–22–10	L. amber acid	1016	V. s. t. nucleo	None	Phenol	None
J. W.	4 years	P.M. 2–22–10	L. amber acid	1018	V. s. t. nucleo	None	Phenol	None
J. L.	2 years	A.M. 11–11–09	Pale acid	1016	None	None	Urobilinogen	Hyaline Cylindroid
J. L.	2 years	A.M. 11–18–09	Amber acid	1023	None	None	Phenol	None
J. L.	2 years	A.M. 11–20–09	L. amber acid	1016	None	None	None	None

GROUP II.—*Children Obtained from the Orthopedic Ward of the University of Pennsylvania, Suffering from Congenital or Acquired Deformities (Other than Tuberculous).*

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
H. H.	3 years	A.M. 1–28–10	L. amber acid	1030	S. t. nucleo	None	None	Uric acid
H. H.	"	P.M. 1–28–10	L. amber acid	1020	V. s. t. nucleo	None	None	None
H. H.	"	A.M. 1–29–10	L. amber acid	1024	V. s. t. nucleo	None	None	Hyaline Cylindroid
H. H.	"	P.M. 1–29–10	L. amber acid	1028	V. s. t. nucleo	None	None	None
F. M.	5 years	A.M. 1–28–10	Amber acid	1022	V. s. t. serum	None	None	None
F. M.	"	P.M. 1–28–10	L. amber acid	1030	V. s. t. nucleo	None	None	Cal. oxalate
F. M.	"	A.M. 1–29–10	L. amber acid	1020	V. s. t. nucleo	None	None	Uric acid
F. M.	"	P.M. 1–29–10	L. amber acid	1020	V. s. t. nucleo	None	None	None
F. M.	"	R. 3– 4–10	D. amber acid	1024	V. s. t. nucleo V. s. t. serum	None	None	None
F. M.	"	M. 3– 4–10	D. amber acid	1030	V. s. t. nucleo	None	None	Hyaline Cylindroid
F. M.	"	P.M. 3– 4–10	Amber acid	1027	V. s. t. nucleo	None	None	None
F. M.	"	R. 3– 5–10	Amber acid	1024	V. s. t. nucleo	None	None	None
L. B.	8 years	A.M. 1–28–10	L. amber acid	1028	S. t. nucleo	None	None	Uric acid
L. B.	"	P.M. 1–28–10	L. amber acid	1030	None	None	None	None
L. B.	"	A.M. 1–29–10	L. amber acid	1024	V. s. t. nucleo	None	None	Not examined
L. B.	"	A.M. 1–31–10	L. amber acid	1028	None	None	None	None
L. B.	"	P.M. 1–31–10	L. amber acid	1026	V. s. t. nucleo	None	None	Uric acid
H. R.	6 years	A.M. 1–29–10	L. amber acid	1030	V. s. t. nucleo	None	None	Hyaline Cylindroid
A. M.	2 years	A.M. 1–10–10	Pale acid	1022	V. s. t. nucleo	None	Indican Phenol	Uric acid Cal. oxalate
R. T.	4 years	A.M. 1–11–10	L. amber acid	1024	V. s. t. nucleo	None	None	Uric acid
A. R. (f)	6 years	A.M. 1–11–10	L. amber acid	1025	S. t. serum	None	Indican Phenol	Uric acid
A. R. (f)	"	R. 3–31–10	Amber acid	1024	V. s. t. nucleo V. s. t. serum	None	Not examin'd	Not examined
A. R. (f)	"	P.M. 3–31–10	L. amber acid	1020	V. s. t. nucleo V. s. t. serum	None	Not examin'd	Hyaline Cylindroid
R. P.	3 years	R. 3–31–10	L. amber acid	1024	None	None	None	Cal. oxalate
L. K. (f)	8 years	R. 3–31–10	L. amber acid	1024	V. s. t. nucleo	None	Indican	None
F. B. (f)	9 years	R. 3–31–10	L. amber acid	1014	V. s. t. nucleo	None	None	Cal. oxalate
S. H. (f)	2 years	R. 3–31–10	Amber acid	1030	V. s. t. nucleo	None	None	Not examined
C. S. (f)	8 years	R. 3–31–10	L. amber acid	1016	V. s. t. nucleo	None	Indican	Hyaline Cylindroid
C. S. (f)	"	P.M. 3–31–10	L. amber acid	1020	V. s. t. nucleo	None	Indican	Uric acid
F. S.	10 years	R. 3–31–10	L. amber acid	1018	V. s. t. nucleo	None	Not examin'd	None
F. S.	"	P.M. 3–31–10	Amber acid	1020	V. s. t. nucleo	None	None	Cylindroid
K. L.	5½ years	P.M. 3–30–10	Amber acid	1028	None	None	None	Uric acid
K. L.	"	R. 3–31–10	Amber acid	1028	V. s. t. nucleo V. s. t. serum	None	None	Cylindroid
G. W.	3 years	P.M. 3–29–10	D. amber acid	1036	V. s. t. nucleo	None	None	An occasional R. B. C.
G. W.	"	R. 3–30–10	D. amber acid	1030	V. s. t nucleo V. s. t. serum	None	None	An occasional R. B. C.
K. D. (f)	7 years	P.M. 3–29–10	D. amber acid	1030	V. s. t. nucleo	None	None	Cal. oxalate None

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
K. D. (f)	7 years	R. 3–30–10	D. amber acid	1028	V. s. t. nucleo	None	Urobilinogen	None
M. H. (f)	"	P.M. 3–29–10	Amber acid	1032	V. s. t. nucleo	None	None	None
M. H. (f)	"	R. 3–30–10	D. amber acid	1032	V. s. t. nucleo	None	None	Not examined
J. C.	3 years	R. 3–29–10	L. amber acid	1032	V. s. t. nucleo	None	None	None
J. C.	"	A.M. 3–29–10	L. amber acid	1026	V. s. t. nucleo V. s. t. serum	None	None	Hyaline Cylindroid
M. G.	10 years	A.M. 12– 9–09	L. amber acid	1020	V. s. t. nucleo	None	None	None
H. A.	3 years	A.M. 12– 9–09	L. amber acid	1027	S. t. nucleo	None	None	Hyaline Cylindroid
A. M.	6 years	A.M. 12– 9–09	L. amber acid	1010	None	None	None	None
M. G.	4 years	A.M. 12– 9–09	L. amber acid	1014	V. s. t. nucleo	None	None	None
W. J.	8 years	A.M. 12– 9–09	L. amber acid	1016	V. s. t. serum	None	None	None
R. R. (f)	10 years	A.M. 12–10–09	Amber acid	1027	V. s. t. nucleo S. t. serum	None	None	Cal. oxalate
F. B. (f)	3 years	A.M. 12–10–09	L. amber acid	1024	S. t. serum	None	None	None
H. D.	5 years	A.M. 12–15–09	D. amber acid	1030	None	None	None	Cal. oxalate
H. K.	5 years	A.M. 12–15–09	Amber acid	1025	None	None	None	Cal. oxalate Amorp. urates
E. C.	7 years	A.M. 12– 9–09	L. amber acid	1022	V. s. t. nucleo	None	None	Cal. oxalate
B. B.	8 years	A.M. 12–10–09	L. amber acid	1026	None	None	None	None
D. B. (f)	2 years	A.M. 12–11–09	L. amber acid	1020	V. s. t. nucleo	None	Phenol	None
D. B (f)	"	A.M. 12–12–09	L. amber acid	1018	V. s. t. nucleo	None	None	None
M. G.	11 years	P.M. 1–28–10	L. amber acid	1022	None	None	None	Not examined
M. G.	"	A.M. 1–29–10	L. amber acid	1024	None	None	None	Uric acid
M. G.	Mixed diet	P.M. 2–24–10	Pale acid	1020	None	None	None	None
M. G.	"	R. 2–25–10	L. amber acid	1020	None	None	None	Hyaline Cylindroid
M. G.	"	A.M. 2–25–10	L. amber acid	1027	V. s. t. nucleo	None	None	Amorp. urates
M. G.	"	M. 2–25–10	L. amber acid	1030	S. t. serum S. t. nucleo	None	Phenol	Amorp. urates
M. G.	"	P.M. 2–25–10	L. amber acid	1014	V. s. t. nucleo	None	None	None
M. G.	"	R. 2–26–10	L. amber acid	1014	V. s. t. nucleo	None	None	Uric acid
M. G.	"	A.M. 2–26–10	Amber acid	1020	S. t. nucleo	None	None	Hyaline Cylindroid
M. G.	"	M. 2–26–10	L. amber acid	1020	S. t. nucleo	None	None	Uric acid
M. G.	"	P.M. 2–26–10	L. amber acid	1025	V. s. t. nucleo	None	None	Uric acid
M. G.	"	R. 2–27–10	L. amber acid	1012	V. s. t. nucleo	None	None	None
M. G.	"	A.M. 2–27–10	L. amber acid	1014	None	None	None	None
M. G.	"	P.M. 2–27–10	L. amber acid	1020	V. s. t. nucleo	None	None	None
M. G.	Milk diet	R. 2–28–10	L. amber acid	1025	V. s. t. nucleo	None	None	None
M. G.	"	A.M. 2–28–10	L. amber acid	1026	S. t. nucleo	None	None	Not examined
M. G.	"	M. 2–28–10	L. amber acid	1025	S. t. nucleo	None	None	None
M. G.	"	P.M. 2–28–10	L. amber acid	1012	None	None	None	None
M. G.	"	R. 3– 1–10	L. amber acid	1012	V. s. t. nucleo	None	None	Not examined
M. G.	"	A.M. 3– 1–10	L. amber acid	1014	None	None	None	None
M. G.	"	M. 3– 1–10	L. amber acid	1020	None	None	None	Not examined
M. G.		P.M. 3– 1–10	L. amber acid	1018	V. s. t. nucleo	None	None	None

GROUP III.—*Children from the Baptist Orphanage of Philadelphia.*

Name.	Age.	Date.	Total amount in c.c.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
W. K.	11 years	24 hours 3–25–10	1020	L. amber acid	1024	V. s. t. nucleo	None	None	None
		A.M. 3–25–10		L. amber acid	1010	V. s. t. nucleo			Uric acid
		M. 3–25–10		L. amber acid	1022	None			Uric acid
		P.M. 3–25–10		Pale acid	1012	None			None
		R. 3–26–10		Amber acid	1926	None			Not examin'd
C. B.	11 years	24 hours 3–25–10	700	L. amber acid	1020	V. s. t. nucleo V. s. t. serum	None	None	Cylindroid
		A.M. 3–25–10		L. amber acid	1028	S. t. serum			
		M. 3–25–10		Amber acid	1030	S. t. nucleo S. t. serum			
		P.M. 3–25–10		L. amber acid	1020	S. t. nucleo			
		R. 3–26–10		L. amber acid	1022	V. s. t. nucleo			
A. S.	11 years	24 hours 3–20–10	650	L. amber acid	1020	V. s. t. nucleo	None	None	Uric acid
		A.M. 3–20–10		L. amber acid	1024	None			
		M. 3–20–10		Pale acid	1016	S. t. serum			
		P.M. 3–20–10		Pale acid	1020	None			
		R. 3–21–10		L. amber acid	1030	None			
W. A.	5 years	24 hours 3–27–10	575	L. amber acid	1017	V. s. t. nucleo	None	Indican	Uric acid
		A.M. 3–27–10		Pale acid	...	V. s. t. nucleo			
		M. 3–27–10		Pale acid	...	V. s. t. nucleo			
		P.M. 3–27–10		L. amber acid	1026	V. s. t. nucleo			
		R. 3–28–10		Pale acid	1012	V. s. t. nucleo			
N. W.	4 years	24 hours 3–15–10	600	L. amber acid	1025	V. s. t. nucleo V. s. t. serum	None	None	None
		A.M. 3–15–10		Pale acid	1028	V. s. t. nucleo			
		M. 3–15–10		Pale acid	1020	V. s. t. nucleo			
		P.M. 3–15–10		Pale acid	1022	S. t. nucleo			
		R. 3–16–10		D. amber acid	1032	S. t. nucleo V. s. t. serum			
C. S.	12 years	24 hours 3–28–10	625						
		M. 3–28–10		Amber acid	1032	None			
		P.M. 3–28–10		Amber acid	1030	V. s. t. nucleo			
C. W.	7 years	24 hours 3–16–10	550	L. amber acid	1028	V. s. t. nucleo V. s. t. serum	None	None	Hyaline Cylindroid
		M. 3–16–10		L. amber acid	1025	V. s. t. nucleo S. t. serum			
		P.M. 3–16–10		L. amber acid	1026	V. s. t. nucleo V. s. t. serum			
		R. 3–17–10		Amber acid	1028	V. s. t. nucleo V. s. t. serum			
E. G.	6 years	24 hours 3–17–10	625	L. amber acid	1023	V. s. t. nucleo	None	Phenol	Uric acid
		M. 3–17–10		Pale acid	1025	V. s. t. nucleo			
		P.M. 3–17–10		Pale acid	1025	V. s. t. nucleo			
		R. 3–18–10		D. amber acid	1030	V. s. t. nucleo			

Name.	Age.	Date.	Total amount in c.c.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
		24 hours		D. amber					
E. C.	5 years	3–18–10	525	acid	1030	V. s. t. nucleo	None	Urobilinogen	Uric acid
		A.M.		L. amber					
		3–18–10		acid	1030	V. s. t. nucleo			
		M.		Amber					
		3–18–10		acid	1029	V. s. t. nucleo			
		P.M.		Amber					
		3–18–10		acid	1028	V. s. t. nucleo			
		R.		D. amber					
		3–19–10		acid	1030	V. s t. nucleo			
		24 hours							
J. S	6 years	3–15–10	450	Pale acid	1023	V. s. t. serum	None	None	None
		A.M.							
		3–15–10		Pale acid	1020	V. s. t. serum			
		M.							
		3–15–10		Pale acid	1025	V. s. t. serum			
		P.M.							
		3–15–10		Pale acid	...	V. s. t. serum			
		R.		D. amber					
		3–16–10		acid	...	V. s. t. serum			
		24 hours							Hyaline
E. W.	5 years	3–17–10	670	Pale acid	1025	V. s. t. nucleo	None	None	Uric acid
		A.M.							
		3–17–10		Pale acid	1022	V. s. t. nucleo			
		M.							
		3–17–10		Pale acid	1024	S. t. nucleo			
		P.M.							
		3–17–10		Pale acid	1025	V. s. t. nucleo			
		R.		L. amber					
		3–18–10		acid	1030	V. s. t. nucleo			
		24 hours		Amber		V. s. t. nucleo			Hyaline
P. K.	6 years	3–16–10	300	acid	1030	V. s. t. serum	None	None	Cylindroid
		M.		Amber		V. s. t. nucleo			Uric acid
		3–16–10		acid	1030	V. s. t. serum			
		P.M.		Amber					
		3–16–10		acid	1030	None			
		R.		Amber					
		3–17–10		acid	1028	V. s. t. nucleo			
		24 hours		L. amber		V. s. t. nucleo			
E G.	7 years	3–15–10	515	acid	1025	V. s. t. serum	None	None	None
		A.M.		L. amber					
		3–15–10		acid	1025	V. s. t. serum			
		M.		L. amber					
		3–15–10		acid	1028	None			
		P.M.		Amber		V. s. t. nucleo			
		3–15–10		acid	1028	V. s. t. serum			
		R.		D. amber		V. s. t. nucleo			
		3–16–10		acid	1035	V. s. t. serum			
		24 hours		L. amber					Hyaline
F. S.	12 years	3–21–10	775	acid	1022	V. s. t. nucleo	None	None	Cylindroid
		A.M.		L. amber					Uric acid
		3–21–10		acid	1020	V. s. t. nucleo			
		M.							
		3–21–10		Pale acid	1012	S. t. nucleo			
		P.M.		L. amber					
		3–21–10		acid	1024	V. s. t. nucleo			
		R.		D. amber					
		3–22–10		acid	1022	V. s. t. nucleo			
		24 hours		L. amber					Hyaline
J. K.	13 years	3–21–10	1250	acid	1025	V. s. t. nucleo	None	None	Cylindroid
		A.M.							Cal oxalate
		3–21–10		.....	...	V. s. t. nucleo			
		M.							
		3–21–10		.....	...	V. s. t. nucleo			
		P.M.							
		3–21–10		.....	...	V. s. t. nucleo			
		R.							
		3–22–10		.....	...	V. s. t. nucleo			
		24 hours		L. amber					
J F.	11 years	3–22–10	600	acid	1020	V. s. t. nucleo	None	None	None
		A.M.		L. amber					
		3–22–10		acid	1030	V. s. t. nucleo			
		M.				V. s. t. nucleo			
		3–22–10		Pale acid	1018	V. s. t. serum			
		P.M.		L. amber					
		3–22–10		acid	1025	V. s. t. nucleo			
		R.		D. amber					
		3–23–10		acid	1025	None			

Name.	Age.	Date.	Total amount in c.c.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
		24 hours		L. amber					
E. A.	11 years	3–22–10	1020	acid	1020	V. s. t. nucleo	None	None	None
		A.M.				V. s. t. nucleo			
		3–22–10		.....	...	V. s. t. serum	None	None	None
		M.							
		3–22–10		.....	...	V. s. t. nucleo	None	None	None
		P.M.							
		3–22–10		.....	...	V. s. t. nucleo	None	None	None
		R.							
		3–23–10		.....	...	V. s. t. nucleo	None	None	None
		24 hours		Amber					
J. H. B.	8 years	3–26–10	500	acid	1030	V. s. t. nucleo	None	Phenol	Amor. urates
		A.M.		Amber					
		3–26–10		acid	1030	None			
		M.							
		3–26–10		.....	...	None			
		P.M.							
		3–26–10		.....	1027	None			
		R.							
		3–27–10		.....	1032	V. s. t. nucleo			
		24 hours		L. amber					Hyaline
R. D.	10 years	3–26–10	650	acid	1020	V. s. t. nucleo	None	Phenol	Cylindroid
		A.M.		L. amber					Uric acid
		3–26–10		acid	1024	V. s. t. nucleo			
		M.		L. amber					
		3–26–10		acid	1026	V. s. t. nucleo			
		P.M.		Amber		S. t. nucleo			
		3–26–10		acid	1022	V. s. t. serum			
		R.		Amber		V. s. t. nucleo			
		3–27–10		acid	1022	V. s. t. serum			
		24 hours		L. amber					
R. T.	8 years	3–26–10	500	acid	1026	V. s. t. nucleo	None	None	Amor. urates
		A M.		L. amber					
		3–26–10		acid	1026	V. s. t. nucleo			
		M.		L. amber					
		3–26–10		acid	1032	None			
		P.M.		Amber					
		3–26–10		acid	1032	S. t. nucleo			
		R.		Amber					
		3–27–10		acid	...	V. s. t. nucleo			
		24 hours		Amber					
E. L.	9 years	3–18–10	600	acid	1028	V. s. t. nucleo	None	None	Amor. urates
		A.M.		Amber					Uric acid
		3–18–10		acid	1028	V. s. t. nucleo			
		M.		L. amber					
		3–18–10		acid	1025	V. s. t. nucleo			
		P.M.		Amber					
		3–18–10		acid	1028	V. s. t. nucleo			
		R.		Amber					
		3–19–10		acid	1028	V. s. t. nucleo			
		24 hours				V. s. t. serum			Hyaline
D. F.	9 years	3–19–10	975	Pale acid	1025	V. s. t. nucleo	None	None	Cylindroid
		A.M.							
		3–19–10		Pale acid	1022	V. s. t. nucleo			
		M.							
		3–19–10		Pale acid	1020	None			
		P.M.		Amber		V. s. t. nucleo			
		3–19–10		acid	1022	S. t. serum			
		R.		Amber		V. s. t. nucleo			
		3–20–10		acid	1030	V. s. t. serum			
		24 hours		Amber		V. s. t. nucleo			
E. A.	7 years	3–16–10	560	acid	1030	V. s. t. serum	None	None	Uric acid
		M.		Amber					
		3–16–10		acid	1028	V. s. t. nucleo			
		P.M.		Amber					
		3–16–10		acid	1030	V. s. t. nucleo			
		R.		Amber					
		3–17–10		acid	1032	V s. t. nucleo			
		24 hours		L. amber		V. s. t. nucleo			
J. C.	9 years	3–19–10	700	acid	1020	V. s. t. serum	None	None	Not examin'd
		A.M.		L. amber		V. s. t. nucleo			
		3–19–10		acid	1022	V. s. t. serum			
		M.							
		3–19–10		Pale acid	1020	V. s. t. nucleo			
		P.M.							
		3–19–10		Pale acid	1021	V. s. t. nucleo			
		R.		L. amber		V. s. t. nucleo			
		3–20–10		acid	1025	V. s. t. serum			

Name.	Age.	Date.	Total amount in c c.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
		24 hours		L. amber		V. s. t. nucleo			
F. B.	7 years	3-19-10	775	acid	1020	V. s. t. serum	None	None	Not examin'd
		A.M.		L. amber					
		3-19-10		acid	1020	V. s. t. nucleo			
		M.							
		3-19-10		Pale acid	1022	None			
		P.M.							
		3-19-10		Pale acid	1025	S. t. nucleo			
		R.		L. amber					
		3-19-10		acid	1028	V. s. t. nucleo			
		24 hours		L. amber					Hyaline
M. A.	8 years	3-27-10	775	acid	1016	V. s. t. nucleo	None	None	Uric acid
		A.M.		L. amber					
		3-27-10		acid	1024	V. s. t. nucleo			
		M.		L. amber					
		3-27-10		acid	1012	V. s. t. nucleo			
		P.M.		L. amber					
		3-27-10		acid	1014	V. s. t. nucleo			
		R.		Amber					
		3-28-10		acid	1018	V. s. t. nucleo			
		24 hours		L amber					
A. P.	10 years	3-27-10	575	acid	1027	V. s. t. nucleo	None	None	Cal. oxalate
		A.M.		L. amber					
		3-27-10		acid	1026	None			
		M.		L. amber					
		3-27-10		acid	1025	None			
		P.M.		Amber					
		3-27-10		acid	1028	V. s. t. nucleo			
		R.		L. amber					
		3-28-10		acid	1025	V. s. t. nucleo			
		24 hours		L. amber		V. s. t. nucleo			
J. B.	10 years	3-20-10	775	acid	1020	V. s. t. serum	None	Phenol	None
		A.M.		L. amber		S. t. nucleo			
		3-20-10		acid	1022	S. t. serum			
		M.		L. amber		S. t. nucleo			
		3-20-10		acid	1018	V. s. t. serum			
		P.M.		Amber		S. t. nucleo			
		3-20-10		acid	1026	V. s. t. serum			
		R.		L. amber					
		3-21-10		acid	1018	V. s. t. nucleo			
				Amber					
	Recumb't			acid	1024	None			
				L. amber					
	Upright			acid	1026	None			
		24 hours		L. amber		T. nucleo			Hyaline
V. D.	7 years	3-18-10	700	acid	1025	S. t. serum	None	None	Cylindroid
		A.M.				V. s. t. nucleo			Uric-acid
		3-18-10		Pale acid	1025	S. t. serum			
		M.				T. nucleo			
		3-18-10		Pale acid	1025	S. t. serum			None
		P M.		Amber		M. t. nucleo			
		3-18-10		acid	1030	M. t. serum			
		R.		Amber					None
		3-19-10		acid	1030	V. s. t. nucleo			
		24 hours		L. amber		T. nucleo			Hyaline
		3-21-10	600	acid	1018	T. serum	None	Indican	Cylindroid
		R.		Amber					Uric acid
		3-21-10		acid	1030	V. s. t. nucleo			Cal. oxalate
		A.M.		Amber		T. nucleo			
		3-21-10		acid	1030	T. serum			None
		M.		L. amber		T. nucleo			
		3-21-10		acid	1020	T. serum			
		P.M.		Amber		M. t. nucleo			None
		3-21-10		acid	1030	M. t. serum			
		R.		Amber		S. t. nucleo			
		3-22-10		acid	1030	S. t. serum			None
		A.M.				V. s. t. nucleo			
	Recumb't	3-22-10		Pale acid	1022	V. s. t. serum			
						V. s. t. nucleo			
	Upright	3-22-10		Pale acid	1020	V. s. t. serum			

Name.	Age.	Date.	Total amount in c.c.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
		24 hours		L. amber		S. t. nucleo			
H. M.	12 years	3-22-10	600	acid	1024	S. t. serum	None	Phenol	None
		A.M.		L. amber					
		3-22-10		acid	1014	None			
		M.		L. amber		T. nucleo			
		3-22-10		acid	1020	M. t. serum			
		P.M.		L. amber		V. s. t. nucleo			
		3-22-10		acid	1030	V. s. t. serum			
		R.		D. amber					
		3-23-10		acid	1026	S. t. nucleo			
				L. amber		S. t. nucleo			
	Recumb't	3-24-10		acid	1026	S. t. serum			
				L amber		S. t. nucleo			
	Upright	3-24-10		acid	1026	S. t. serum			
		24 hours		L. amber					
E. S.	3 years	3-24-10	550	acid	1022	V. s. t. nucleo	None	None	None
		A M.		L. amber					
		3-24-10		acid	1022	None			
		M.							
		3-24-10		Pale acid	1008	None			
		P.M.		L. amber					
		3-24-10		acid	1025	None			
		R.		L. amber					
		3-24-10		acid	1025	V. s. t. nucleo			
		24 hours		L. amber					
F. M.	8 years	3-24-10	550	acid	1024	V. s. t. nucleo	None	None	None
		A M.		L. amber					
		3-24-10		acid	1023	V. s. t. nucleo			
		M.		L. amber					
		3-24-10		acid	1026	S. t. nucleo			
		P.M.		Amber					
		3-24-10		acid	1032	S. t. nucleo			
		R.		Amber					
		3-25-10		acid	1030	V. s. t. nucleo			
		24 hours		L. amber					
H. W.	12 years	3-24-10	1000	acid	1020	V. s. t. nucleo	None	None	None
		A.M.		L. amber					
		3-24-10		acid	1022	None			
		M.							
		3-24-10		Pale acid	1008	None			
		P.M.		L. amber					
		3-24-10		acid	1025	None			
		R.		L. amber					
		3-24-10		acid	1025	V. s. t. nucleo			
		24 hours		L. amber					
R. H.	12 years	3-23-10	700	acid	1024	V. s. t. nucleo	None	None	None
		A.M.		L. amber					
		3-23-10		acid	1024	V. s. t. nucleo			
		M.		L. amber					
		3-23-10		acid	1024	V. s. t. nucleo			
		P.M.		Amber					
		3-23-10		acid	1030	None			
		R.		Amber					
		3-24-10		acid	1032	None			
		24 hours		L. amber		S. t. nucleo			
C. B.	7 years	3-28-10	475	acid	1022	V. s. t. serum	None	None	Amor. urates
		A.M.		L. amber		M. t. nucleo			
		3-28-10		acid	1022	T. serum			None
		M.		L. amber		S. t. nucleo			
		3-28-10		acid	1022	S. t. serum			None
		P.M.		L. amber		S. t. nucleo			
		3-27-10		acid	1020	V. s. t. serum			None
		R.		Amber		S. t. nucleo			
		3-28-10		acid	1030	V. s. t. serum			None
		24 hours		L. amber					
R. M.	9 years	3-28-10	500	acid	1022	None	None	None	None
		A.M.		L. amber					
		3-28-10		acid	1020	V. s. t. nucleo			
		M.		L. amber					
		3-28-10		acid	1022	V. s. t. nucleo			
		P.M.		L. amber					
		3-28-10		acid	1022	V. s. t. nucleo			
		R.		L. amber					
		3-29-10		acid	1020	V. s. t. nucleo			

GROUP IV.—*A Group of Three Children, whose Urines were Examined Practically Every day for Several Weeks.*

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
H. H.	8 years	A.M. 11– 1–09	Pale acid	1024	V. s. t. serum	None	None	None
		A.M. 11– 2–09	Pale acid	1022	V. s. t. serum	None	None	Cal. oxalates
		A.M. 11– 3–09	L. amber acid	1024	V. s. t. serum	None	None	Uric acid Cal. oxalates
		A.M. 11– 4–09	L. amber acid	1026	V. s. t. nucleo V. s. t. serum	None	None	None
		A.M. 11– 5–09	L. amber acid	1020	S. t. serum S. t. nucleo	None	Phenol	None
		A.M. 11– 6–09	L. amber acid	...	V. s. t. nucleo	None	None	Uric acid Cal. oxalates
		P.M. 11– 7–09	D. amber acid	1022	S. t. nucleo	None	None	Hyaline Cylindroid
		A.M. 11– 8–09	L. amber acid	1023	None	None	None	Uric acid None
		A.M. 11– 9–09	L. amber acid	1023	V. s. t. nucleo	None	None	None
		A.M. 11–10–09	L. amber acid	1020	V. s. t. nucleo V. s. t. serum	None	None	None
		A.M. 11–12–09	L. amber acid	1026	V. s. t. nucleo	None	None	None
		24 hours 11–15–09	L. amber acid	1023	V. s. t. nucleo V. s. t. serum	None	None	None
	950 c.c.	P.M. 11–15–09	L. amber acid	1020	None	None	None	None
		P.M. 11–17–09	Amber acid	1030	S. t. nucleo	None	None	None
		A.M. 11–17–09	Pale acid	1028	S. t. nucleo	None	None	None
		A.M. 11–18–09	D. amber acid	1027	S. t. serum	None	None	Cal. oxalates
		P.M. 11–18–09	L. amber acid	1025	T. nucleo	None	None	Uric acid
		A.M. 11–19–09	Amber acid	1022	T. nucleo S. t. serum	None	None	Uric acid Cal. oxalates
		A.M. 11–20–09	L. amber acid	1025	S. t. nucleo	None	None	None
		24 hours 11–22–09	D. amber acid	1010	V. s. t. nucleo	None	None	Cal. oxalates
	1050 c.c.	A.M. 11–23–10	L. amber acid	1026	V. s. t. nucleo	None	None	None
		A.M. 11–24–10	L. amber acid	1022	V. s. t. nucleo S. t. nucleo	Not exam	Not examin'd	Not examined
		M. 11–26–10	Pale acid	1022	S. t. serum	None	None	Amorp. urates
		A.M. 11–27–10	L. amber acid	1020	S. t. nucleo	None	None	Cal. oxalates
		P.M. 11–27–10	L. amber acid	1024	S. t. nucleo	None	None	Amorp. urates
		M. 12– 2–09	L. amber acid	1022	V. s. t. nucleo	None	None	Uric acid
		M. 12– 3–09	Pale acid	1020	V. s. t. nucleo	None	None	None
		A.M. 12– 4–09	L. amber acid	1020	V. s. t. nucleo	None	None	Cal. oxalates
		M. 12– 5–09	L. amber acid	1022	V. s. t. nucleo	None	None	None
		A.M. 12– 6–09	L. amber acid	1024	V. s. t. nucleo	None	None	None
McC. H.	10 years	A.M. 11– 1–09	L. amber acid	1020	None	None	None	None
		A.M. 11– 2–09	D. amber acid	1028	V. s. t. nucleo V. s. t. serum	None	None	None
		A.M. 11– 3–09	L. amber acid	1028	None	None	None	Amorp. urates
		A.M. 11– 4–09	L. amber acid	1026	V. s. t. nucleo V. s. t. serum	None	Indican	Uric acid

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
McC. H.	10 years	A.M. 11- 5-09	L. amber acid	1026	V. s. t. nucleo	None	None	None
		A.M. 11- 6-09	L. amber acid	1024	None	None	None	None
		P.M. 11- 7-09	D. amber acid	1021	None	None	None	Uric acid Amorp. urates
		A.M. 11- 8-09	L. amber acid	1021	V. s. t. nucleo V. s. t. serum	None	None	Uric acid Cal. oxalates
		M. 11- 9-09	L. amber acid	1024	S. t. nucleo	None	None	Cal. oxalates
		A.M. 11-10-09	D. amber acid	1022	S. t. nucleo	None	None	Hyaline Cylindroid Uric acid
		A.M. 11-12-09	L. amber acid	1023	V. s. t. nucleo V. s. t. serum	None	None	Cal. oxalates Cal. oxalates
	975 c.c.	24 hours 11-15-09	L. amber acid	1020	None	None	None	None
		P.M. 11-16-09	L. amber acid	1020	None	None	None	Cal. oxalates
		P.M. 11-17-09	L. amber acid	1020	V. s. t. nucleo	None	None	Uric acid
		A.M. 11-17-09	L. amber acid	1022	None	None	None	Cal. oxalates
		A.M. 11-18-09	L. amber acid	1020	V. s. t. nucleo V. s. t. serum	None	None	Uric acid
		P.M. 11-18-09	L. amber acid	1018	V. s. t. nucleo V. s. t. serum	None	None	Cylindroid Uric acid
		A.M. 11-19-09	D. amber acid	1027	V. s. t. nucleo V. s. t. serum	None	None	Amorp. urates Uric acid
		A.M. 11-20-09	L. amber acid	1024	V. s. t. nucleo	None	None	None
	975 c.c.	24 hours 11-22-09	L. amber acid	1022	V. s. t. nucleo V. s. t. serum	None	None	Uric acid
		A.M. 11-23-09	L. amber acid	1027	V. s. t. nucleo	None	None	Amorp. urates Cal. oxalates
		A.M. 11-24-09	L. amber acid	1022	None	Not exam	Not examin'd	Not examined
		A.M. 11-27-09	L. amber acid	1024	S. t. nucleo	None	None	None
		M. 12- 2-09	L. amber acid	1022	None	None	None	Amorp. urates
		P.M. 12- 2-09	L. amber acid	1021	None	None	None	Not examined
		A.M. 12- 4-09	L. amber acid	1024	S. t. serum	None	Not examin'd	None
		A.M. 12-18-09	L. amber acid	1022	V. s. t. nucleo	None	None	None
		P.M. 1-20-10	Amber acid	1027	None	None	None	None
		M. 12-18-10	L. amber acid	1024	None	None	None	Cal. oxalates
		M. 12-19-10	L. amber acid	1020	V. s. t. nucleo	None	Indican	None
K. H.	12 years	A.M. 11- 1-09	L. amber acid	1018	None	None	None	Cal. oxalates
		A.M. 11- 2-09	L. amber acid	1018	None	None	None	None
		A.M. 11- 3-09	L. amber acid	1020	V. s. t. nucleo	None	None	Uric acid Cal. oxalates
		A.M. 11- 4-09	L. amber acid	1020	S. t. nucleo S. t. serum	None	Indican	Uric acid Cal. oxalates
		P.M. 11- 5-09	L. amber acid	1024	V. s. t. nucleo V. s. t. serum	None	None	Uric acid
		A.M. 11- 6-09	L. amber acid	1024	None	None	Indican	Hyaline Cylindroid Amorp. urates Cal. oxalates
		P.M. 11- 7-09	L. amber acid	1018	V. s. t. nucleo	None	Indican	Cal. oxalates
		A.M. 11- 8-09	L. amber acid	1020	None	None	None	Uric acid Cal. oxalates
		A.M. 11- 9-09	L. amber acid	1020	V. s. t. nucleo V. s. t. serum	None	None	None

Name.	Age.	Date.	Color reaction.	Specific gravity.	Albumin.	Sugar, diacetic acid, acetone.	Indican, urobilinogen, phenol.	Casts, cylindroids, crystals.
K. H.	12 years	A.M. 11–10–09	L. amber alkaline	1020	None	None	None	Earthy phos.
		A.M. 11–12–09	L. amber acid	1020	V. s. t. nucleo	None	None	Uric acid
	1950 c.c.	24 hours 11–15–09	L. amber acid	1018	None	None	None	None
		P.M. 11–15–09	L. amber acid	1023	None	None	Indican	None
		P.M. 11–16–09	L. amber acid	1028	V. s. t. nucleo V. s. t. serum	None	None	None
		A.M. 11–17–09	Pale acid	1020	V. s. t. nucleo V. s. t. serum	None	None	Hyaline Cylindroid
		P.M. 11–17–09	Pale acid	1030	V. s. t. nucleo V. s. t. serum	None	None	Uric acid
		P.M. 11–18–09	Pale acid	1030	V. s. t. nucleo	None	None	Amorp. urates
		A.M. 11–19–09	Amber alkaline	1024	None	None	None	Earthy phos.
		P.M. 11–19–09	Amber acid	1028	V. s. t. nucleo	None	None	Amorp. urates Cal. oxalates
		A.M. 11–20–09	L. amber acid	1030	S. t. nucleo	None	None	Amorp. urates Cal. oxalates
	1875 c.c.	24 hours 11–22–09	Amber acid	1020	None	None	None	Cal. oxalates
		A.M. 11–23–09	L. amber acid	1022	V. s. t. nucleo	None	Phenol	Uric acid
		A.M. 11–24–09	Amber acid	1025	V. s. t. nucleo	None	Not examin'd	Cylindroid
		M. 11–26–09	L. amber acid	1030	S. t. nucleo	None	Not examin'd	Cylindroid
		A.M. 11–27–09	Amber acid	1024	V. s. t. nucleo	None	None	Uric acid Hyaline Cylindroid
		M. 12– 2–09	L. amber acid	1027	V. s. t. nucleo	None	None	Uric acid Cal. oxalates Uric acid
		P.M. 12– 2–09	L. amber acid	1022	None	None	None	Cal. oxalates
		A.M. 12– 4–09	L. amber acid	1026	None	None	None	None
		M. 12– 5–09	L. amber acid	1024	V. s. t. nucleo	None	None	Not examined
		A.M. 12– 6–09	L. amber acid	1026	V. s. t. nucleo	None	Indican Phenol	None
		P.M. 12– 6–09	L. amber acid	1022	V. s. t. nucleo	None	None	None
		P.M. 12– 8–09	D. amber acid	1030	V. s. t. nucleo	None	None	None
		A.M. 12– 9–09	L. amber acid	1022	V. s. t. nucleo	None	None	Not examined
		A.M. 1– 7–10	L. amber acid	1020	V. s. t. nucleo	None	None	None
		P.M. 2–14–10	Amber acid	1026	V. s. t. nucleo	None	None	None

KEY.

(f) indicates female. A.M. indicates morning specimens. M. indicates noon specimens. P.M. indicates afternoon specimens. R. indicates specimen voided immediately after a night's rest. 24 hours indicates total amount of urine voided in 24 hours.

ALBUMIN.—V. s. t. means very slight trace of albumin. S. t. means slight trace of albumin. T. means trace of albumin. M. t. means marked trace of albumin.

The form of casts and crystals is indicated by "hyaline," "uric acid," "cal. oxalate," etc.

DISCUSSION.

Dr. S. J. Meltzer: It seems to be an established fact that the mucous membrane of the gastro-intestinal tract is more permeable in children than in adults. This applies perhaps to all mucous membranes. It seems plausible to assume that during the time of rapid growth mucous membranes are more permeable —to facilitate absorption and elimination.

Dr. C. L. Greene: I wonder if one could not consider the causes of this condition, the presence of serum albumin, in a more intelligent way in the light of the work done by Stiller, of Budapest, in congenital universal asthenia. In many cases such a person had what he called physical habits. In dealing with children, they present congenital structures which are anomalous and characterized by their delicate bones, and particularly by what is called the stigma of the disease, a loosened costal belt and movable tenth rib. This sort of cases later on, according to Stiller, present gastric neuroses and the common forms of neurasthenia. He claims that practically all children show serum albumin in the urine without any evidence of active renal lesions and stigmata of congenital universal asthenia might be found.

PRELIMINARY NOTE ON MEDICAL USES OF RECTAL INFUSIONS.

By HENRY SEWALL, M.D.,
DENVER, COLORADO.

The use of the lower bowel as a channel for the introduction of fluids into the body dates back to early days in medicine, but since the rational application of the method was devised by J. B. Murphy,[1] it has become one of the salient procedures in postoperative surgical therapeutics. It is not surprising that the practice of proctoclysis, which has become well nigh routine in the surgical clinic, should promise to assume a definite place in the wider field of medical treatment. But the procedure must degenerate into mechanical manipulation unless the indications for its service and the limitations of its usefulness are established by critical observation. An intelligent application of the method presupposes a definite notion of its mode of action and of the objects to be accomplished. From a theoretical point of view the following summary may be made of the distinctive vital relations of proctoclysis: (1) Rectal infusions would seem less disturbing to the economy than fluid offered to the body through any other channel. Fluid introduced into the lower bowel by the "Murphy method" produces a minimum of peristaltic reaction, and its absorption is probably regulated by the vital demands of the organism. (2) Warm rectal infusions have a diuretic effect, which is frequently immediate and intense. In certain cases the amount of fluid expelled from the body by diuresis greatly exceeds that introduced by proctoclysis. (3) Soluble toxines proceeding from loci of infection impair the vitality and reduce the resistance power of the healthy tissues through which they circulate.

[1] J. B. Murphy, Perforative Peritonitis, Surgery, Gynecology, and Obstetrics, June, 1908.

The surgeon has a lively sense of the gravity of this incident as influencing tissue repair and general reaction after operation. The condition is no less important in medical cases of disease. Dilution of the circulating toxines with imbibed fluid and their removal by diuresis would seem not only to protect the kidneys by lessening the concentration of the poisons excreted, but tend to safeguard the sound tissues from intoxication. (4) Clinical observation indicates that microbic metastasis is prone to seek out regions where tissues have already been injured by circulating toxines. Thus, in gonorrheal infection, there is reason to believe that joint pains due to transported toxines are apt to precede the local establishment of the cocci. Proctoclysis appears to ameliorate such pains and, inferentially, limit extension of the infection. (5) The addition of foreign fluid to the circulation is an important aid to the maintenance of a normal arterial blood pressure, possibly not so much by reason of the volume of fluid added as by reducing intoxication of the mechanism of circulation. (6) The exhibition of many medicines by way of rectal infusions commends itself as free from obvious disadvantages inherent to the oral channel.

For many years I have occasionally applied one or another method of proctoclysis in the medical clinic, but only during the past year has the method been somewhat systematically pursued according to the principles of Murphy's technique. In my observations the attempt has purposely been made to achieve results with the aid of such simple apparatus as is available in any bedroom. It is probable that the results would have been more satisfactory with a more adequate equipment. The fluid infused was either tap water or normal saline, as the condition of the patient seemed to demand. One or two pints of fluid, rather hot to the touch, would be placed in the bag of a "fountain syringe" and introduced into the rectum through the hard rubber tip commonly used for enemata. The bag was usually suspended so that the surface of fluid within it should be elevated four to eight inches above the anus. The bag is raised or lowered according to the rate of outflow or complaints of the patient. Nearly two pints of fluid should flow out in the course of an hour. With this simple apparatus considerable difficulty is experienced from the cooling of the fluid in the outflow tube.

This is partly remedied by keeping the tube under the bedclothes, or occasionally withdrawing the tip and allowing the cooled fluid to run off. The temperature in the reservoir may be maintained by the addition now and then of small quantities of very hot water or saline. As is well known, the essence of Murphy's method lies in the free communication between the rectum and reservoir, with the hydrostatic balance so slightly in favor of the latter that, while fluid surely gravitates toward the bowel, a slight excess of pressure within the rectum is relieved by a reversal of the current into the reservoir. The head of pressure in the reservoir should be so low that the distention occasioned by the flow should neither provoke contraction of the gut nor cause perceptible reaction of the anal sphincter. The special form of outflow tip, having a sharp bend in its course, which Murphy devised for patients treated in the Fowler position, does not seem necessary in medical cases that lie supine.

In my experience proctoclysis pursued in this manner is not always so indifferent to the comfort of patients as surgeons seem to find. Both the mechanical relations of the Fowler's position and the psychic distraction of a surgical injury probably combine to facilitate the application of the method in operative cases. With medical subjects it is often difficult to adjust the apparatus so as to avoid discomfort. The nurse is prone to raise the reservoir of fluid too high.

In practice it has been my habit to judge the utility of the method largely by the reaction of the kidneys. Abundant diuresis has been accepted as a sign of the efficiency of the procedure, or *vice versa.* Instead of continuous proctolysis, as commonly employed by the surgeon, I have usually sought the absorption of a quart of fluid twice a day—in forenoon and afternoon.

The cases on which this article is based may be divided into two groups: (1) those in which it is desired to raise arterial blood pressure, or, by stimulating diuresis, to deplete an effusion; (2) those in which it is endeavored to reduce a toxemia.

In the first group, two cases gave such striking results as to form a basis for further observation. One was that of a man of middle age, probably an old alcoholic, prostrated with an asthenia of uncertain origin. Proctoclysis to the extent of two quarts of saline daily

seemed an important aid to his gradual recovery. The other was that of a man, aged about sixty years, with pleural effusion, general dropsy, and orthopnea of myocardial origin. Hot water given by the "drop method" resulted in a progressive diuresis, which in a few days removed the dropsy and led to recovery of cardiac compensation. Other attempts to reduce dropsical effusions by proctoclysis have not been so successful, but the conclusion, from a considerable experience, favors the exhibition of hot water by the bowel in an effort to reduce dropsical accumulations which do not yield to other remedies. Of course, a comparison of the volume of fluid absorbed with that excreted quickly determines the availability of the method.

But it is the second class of cases, those suffering from constitutional toxemia, which offers the most pertinent field for proctoclysis. Already the method has been advocated, more or less modified, in the treatment of typhoid fever and of scarlet fever. Durbin[1] has long used colonic saline irrigations with favorable results in the treatment of typhoid fever, and Riesman[2] has recently reported satisfactory results obtained by the Murphy method. My own experience with proctoclysis in this disease has also been favorable, but is based on only a half dozen cases. In a similar number of cases of lobar pneumonia, one of which was in an alcoholic with extensive lung involvement, high temperature and wild delirium, I have been much impressed with the favorable effects when proctoclysis with hot tap water was made a therapeutic measure.

The procedure was usually followed in a few hours by an abatement of the signs of toxemia, and especially by improvement in the mental condition. Indeed, no class of cases has been more obviously ameliorated than that suffering from delirium. I have been struck with the rapid clearing up of the mental condition in obstinate cases of delirium tremens encountered in my wards of the Denver County Hospital. The resident interne assisting me, Dr. Elizabeth M. Collier, has continued the application of the method in such subjects since the lapse of my term of service and reports very favorable results from it.

I have used saline infusions in four cases of scarlet fever, two of

[1] Denver Medical Times and Utah Med. Jour., July, 1909.
[2] Jour. Amer. Med. Assoc., January 29, 1910.

them very severe, and the results were admirable. The casts and albumin found in the urine early in the disease disappeared before the patients were ready to leave their beds.

In functional disorders, marked by acetonuria, great gastric irritability, and depression of renal activity, proctoclysis and the administration of bicarbonate and salicylate of soda by rectal infusion have proved of great value.

In a number of cases of chronic pulmonary tuberculosis, having a daily rise of temperature, I have failed to see decided benefit from proctoclysis. But in the intercurrent febrile, "grippal" attacks, the comfort of the patient has been greatly increased and the invasion apparently cut short by the procedure. In the sudden flooding of the system with toxines from confined pus, which not rarely occurs in tuberculous subjects, remarkable amelioration of the symptoms may follow saline infusion of the bowel.

In conclusion, it must be admitted that the favorable results accompanying the use of proctoclysis in appropriate medical cases indicate that this method of *quasi* internal hydrotherapy deserves such a thoroughly detailed study as will accurately establish its indications and limitations in medical therapeutics.

A CASE OF FATAL SODIUM CHLORIDE POISONING, WITH A BRIEF STUDY OF THE EFFECTS OF THE EXCESSIVE ADMINISTRATION OF SALT ON THE TISSUES.

By HARLOW BROOKS, M.D.,
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All are more or less familiar with the effects which follow the excessive administration of sodium chloride, especially with those of minor grades which arise, for example, after the ingestion of meats or other foods highly salted, or after drinking water rich in sodium chloride. Indeed, it is highly probable that death which is stated to occur soon when, other water lacking, sea water is taken as a beverage, is due, for the most part, to the direct action of the salt and its effect on the tissues of the body. When, through choice or necessity, salt foods are taken largely, and when, at the same time, one is unable to secure the requisite amount of water which nature demands in this condition, symptoms arise illustrative of the effects of excessive amounts of NaCl. This is a fact well appreciated by frontiersmen, explorers, soldiers, by the primitive races, and even by the lower animals, to a certain degree. The cure of these conditions, when nature is allowed her way, is automatically brought about by the taking of water until the oversaturation of the tissues and body fluids is reduced to, or near, normal.

In death from thirst, especially when associated with a high external temperature, thus favoring the rapid evaporation of the liquids of the body through the excretory tracts, it is also highly probable that the fatal end is, in part, brought about as a result of the concentration of the salts, largely NaCl, in the blood and tissues.

Instances of serious results following the injection of concentrated

solutions locally are not so very infrequent, and in the haste and excitement of emergency surgery, several times within my knowledge it has happened that a too strong saline was mistakenly used instead of one of normal strength. The results in these cases have commonly been local death of tissue, sometimes with extensive sloughing or subsequent abscess formation, but usually entirely without general symptoms. It is also possible that some of the deaths which have followed saline venous infusion may have accidentally occurred in this manner, a possibility rather unlikely to be detected in these instances when ordinarily the pre-existing symptoms and conditions are of so severe a grade as to render death not unexpected; therefore, a searching inquiry would probably not be instituted.

Much experimental work has been done as to the effects of concentrated saline on the body, chiefly along physiological and pharmacological lines. In some instances these experiments have been conducted with sodium chloride, but in most the heavy salts, notably those of magnesium or the other saline cathartics, have been employed. It is practically certain that most of these substances act very largely as does NaCl similarly introduced, and the changes effected in the tissues experimentally are very similar.

It has been quite universally accepted that most of the salines poison or act through alterations in the intracorpuscular osmotic processes. Of late, work along these lines by improved methods, notably the researches of Meltzer and his school, have demonstrated that, in addition to this well established reaction, there is a definite individual toxic effect, depending on and varying with the metallic ion employed in each instance. In regard, however, to the toxic action of sodium chloride, most observers state that it is purely and entirely one of osmotic disturbance, a fact which Joseph and Meltzer[1] also admit has not been disproved by their experiments designed to elucidate this point, although these authors, nevertheless, apparently mean to suggest their personal belief somewhat to the contrary. As a result of this last mentioned research it has been shown that sodium chloride is the least toxic of the group of similar metal chlorides, possibly partly due to its lesser molecular weight. For

[1] Journal of Pharmacology and Experimental Therapeutics, June, 1909.

dogs, Joseph and Meltzer established a dose of 63 c.c. of NaCl per kilo of body weight; but, as those authors patently suggest, this applies to dogs only, and the experiments, for example, of Loeb have shown a greater degree of toxicity toward the eggs of Fundulus.

In so far as I have been able to ascertain, the following case of human poisoning by salt is entirely unique in medical literature, notably in the fact that the drug was introduced in this case through the intestine, and that it produced speedy death. I have, therefore, considered the instance important enough to report to this body, together with a very brief study, designed to verify the conclusions as to the cause of death and to demonstrate, in so far as possible, the manner in which this end was probably brought about.

The case was personally reported to the writer by Dr. W. T. Bivings, of Atlanta, Georgia.

A vigorous young woman, of about 124 pounds weight, was operated on during the quiescent period for chronic appendicitis. The operation was in every way successful, and the patient left the table in twenty minutes. After forty minutes she had fully recovered from the anesthetic. Postoperative pulse, respiration, and temperature practically normal.

A rectal enema, composed of 1 pint normal saline and ½ oz. whisky, was ordered to be repeated q.i.h. for three doses.

One hour after the first enema the patient became quite restless and nervous and complained of thirst. At the second dose, these symptoms became more exaggerated, and she begged continuously for the bed-pan. The condition was then reported to the surgeon; a third enema was, however, given before his arrival, when he found the patient unconscious. Pulse small, 120; temperature, 101° F. The pupils were contracted and failed to react to light. The conjunctiva was injected, and tears poured copiously from the eyes.

The temperature rapidly rose to 109° F. (rectal), the respirations became very rapid, shallow, and difficult, the pulse quick and small. She died about eight hours after leaving the table. Forty minutes before death she had a convulsive seizure lasting ten minutes. A few minutes before death about one quart of blood-stained gelatinous material was discharged from the gut. Respiration ceased five minutes before radial and cardiac pulsation.

Urine had been frequently voided during the attack, it showed an average specific gravity of 1.015. No sugar and no albumin was present.

Several days afterward it was discovered that the nurse, who had been appointed to the case by the family, had, instead of normal saline, given enema of nearly saturate sodium chloride, provided and labelled in the operating room as a "stock solution." The patient had thus received nearly 9 oz. of NaCl.

After fully considering the case, with a study of the physiological effects of concentrated saline solutions on the organism, the other possibilities having been apparently eliminated, it was concluded that the cause of death was the concentrated saline, the action of which was probably accentuated by the natural reduction of body resistance consequent upon the operation.

Certain of the conditions manifested by this patient particularly substantiate this assumption. The rapid and high elevation of temperature is characteristic of those disease conditions in which the fluids of the body are rapidly reduced, as, for example, in acute dysentery and in cholera.

The active lacrymation and the diuresis are also cardinal symptoms in the picture following oversaturation of the body fluids with salt, acting, according to some, by stimulation of the glandular cells, as by caffeine, but more likely, as Cushny states, acting on the kidney by the elevation of the capillary pressure of the glomeruli.

The convulsive attacks were doubtless caused by the withdrawal of fluid from the central nervous system and also by direct effects of this abnormal osmosis on the ganglion cells. The succeeding comatose state is similarly explained, though perhaps partly also by the "curare-like action" of sodium chloride on the motor nerve endings, as proposed by Joseph and Meltzer.

I believe that special corroborative stress may also be laid on the fact that respiration ceased in this patient before the heart action, a sign observed in all instances of sodium chloride poisoning by Joseph and Meltzer.

That the probable relationship between the administration of the concentrated saline and the symptoms in this case might be further shown, and the precise way in which the chemical effected the tissues

demonstrated, the following experiments were conducted by Dr. D. M. Kaplan and myself:

Rabbits were chosen for the experimentation, both on account of the facility with which they might be handled, and also because this animal, which rarely or never regurgitates, appears therefore to be most available for tube feeding. Preliminary experiments on dogs, cats, and rabbits soon demonstrated that direct imitation of the conditions pertaining in the case were not practical, as the colon rapidly ejected the concentrated solution. The saline was therefore introduced by the stomach tube.

Experiment I. "Young rabbit, weighing 2 pounds 14 ounces, selected. Ten grams of NaCl dissolved in 25 c.c. of water was introduced by the tube into the stomach of the fasting rabbit. Five minutes later the animal voids 33 c.c. of clear, albumin-free urine. The animal is restless, the breathing shallow, the ears pale. It falls down in a semiconvulsive attack, but regains station, to again sink on haunches. It appears as though suffering from colic; rises, then falls. After fifteen minutes, voids 15 c.c. of urine, which subsequent examination demonstrates to be natural, except for a very high chloride content. One hour after the dose, the animal still shows symptoms of restlessness and abdominal pain, and, at times, of convulsive seizures. Passes 9 c.c. of urine similar to previous specimen, except that the content of NaCl was found to be still greater.

The animal becomes unconscious; the comatous condition being interrupted from time to time by a constant fine muscular tremor and by convulsive seizures. The respiration becomes shallow and very much slowed. The ears are very pale and the peripheral circulation very slight. The heart sounds still remain regular, but very rapid and weak."

One hour and seven minutes after the NaCl had been given the animal died in a convulsion of slight severity.

Fifty-seven cubic centimeters of urine in all was passed between the time of dosage and that of death. The specimens, examined quantitatively, showed a progressive increase of NaCl, but no other evidences of disease.

The postmortem examination showed the peritoneal cavity to

contain a considerable quantity of semigelatinous lymph. The entire gut was distended with a thick, gelatinous mucoid secretion and numerous minute hemorrhagic extravasations were found in the submucosa. The stomach was similarly filled with gelatinous mucus, slightly blood-stained, and considerable areas of submucous extravasation were present, marked by large areas of clotted blood.

The liver tissue was grossly normal. The kidneys were edematous and anemic, but otherwise normal. The heart was relaxed and contained a small amount of dry clotted blood. The muscle walls are apparently edematous. The lungs are notably bloodless; otherwise normal. The skeletal muscles are dry and the bloodvessels throughout filled by a scant dry clot, with notably diminished fluid. The encephalon is anemic, tissue somewhat edematous.

Microscopic examination shows no apparent alteration, either in the tubules or in the glomeruli of the kidney. The bloodvessels are moderately filled by apparently unchanged blood cells and the tissue throughout appears to be normal.

The liver shows a marked alteration in the gland cells, especially in those most adjacent to the sublobular radicles. The change consists in a thinning out of the protoplasmic structure, resulting in a washed-out appearance similar to that seen in very marked edema. All except the finely granular elements of the cell cytoplasm appears to have been washed away. No vascular or interstitial alterations are apparent.

The cells of the heart muscle appear in some areas swollen and edematous; in other places the fibers appear shrunken and desiccated, as though hardened rapidly in too intense fixative.

In places the mucosa of the stomach shows a complete necrosis of the tubules, as though from the action of some strong escarotic; the hemorrhagic extravasations are present, both in the submucosa and in the mucosa, and are, of course, associated with extensive acute destruction of the adjacent tissues. The submucosa is infiltrated with an edematous exudate, which has torn apart and separated the fibrils of the submucosa. In some areas aside from the submucous edema the structure is apparently normal.

Sections through the cerebrum show an almost universal dilatation of the perivascular lymph spaces, with alternating areas of apparent

desiccation and edema in the diffuse tissue. Many of the ganglion cells are atrophied, shrunken, and chromatophylic, as though from fixation in a too rapid and too strong hardening agent. In a few areas the cells appear to be acutely swollen and almost disintegrated.

Experiment II. A full-sized adult rabbit, weighing 4 pounds 9 ounces, was given 20 grams of NaCl in 40 c.c. of water, introduced into the stomach through the tube. "Symptoms appear in fifteen minutes: rapid and shallow breathing, with great restlessness, being first noticed. After thirty-five minutes, very marked peristalsis can be noted through the abdominal walls, which have meantime become somewhat distended. Urine is passed at frequent intervals though in small quantities. Comatous attacks alternate with great restlessness, and at times the animal appears to be in pain, or much frightened; at other times, so somulent as to be almost anesthetic. Convulsive attacks of slight degree and an almost constant muscular tremor is apparent. The breathing is constantly labored."

The animal finally died in a convulsive seizure one hour and forty-five minutes after the dose had been administered. During this time a total of 36 c.c. of highly colored urine was passed. No albumin was present, no blood or casts, but it showed a progressive and finally a very marked increase in the chlorides, and the last specimens are of very high specific gravity.

The postmortem showed a very early and marked degree of postmortem rigidity. The abdomen was markedly distended and the peritoneal cavity contained a considerable amount of gelatinous, slightly blood-stained lymph. The colon was found normal, but the small intestine was distended with gelatinous mucus, not blood-stained, however, and no extravasations were apparent in the walls of the intestine. The stomach was much distended with gas and with blood-stained mucus; this distention was so marked as to cause minute rents to appear in the muscular wall. Large areas of escharotic tissue and of submucous hemorrhage were apparent in the mucosa. The liver showed no gross change, but the kidneys appeared very edematous. The lungs were notably dry—a condition also very marked in the skeletal muscles—but marked edema of the heart muscle and of the encephalon was apparent.

"Microscopic examination shows very marked edematous swelling

of the liver cells, much more marked about the central veins, a few areas of small round cell infiltration adjoining the interstitium, and a notably diminished amount of blood in the venules and capillaries.

"The kidneys show marked edema, with disintegration of the cells of the convoluted tubes in particular. The outlines of the cells are indistinct, the cytoplasm very granular and edematous in appearance, and many of the tubules are nearly filled by a granular cell detritus. No changes are apparent in the glomeruli and nothing abnormal could be recognized in the bloodvessels. The heart cells show shrinkage of the fibers in places and edematous swelling in others. The lymph spaces are apparently much dilated. There is an almost complete necrosis of the upper layers of the gastric mucosa, extensive patches in which the ischemia extends down to the basement membrane. The hemorrhagic extravasations extend from the submucosæ to the upper surfaces of the mucosa in the most extensively involved areas. There is a general edema of the submucosa throughout.

"There is a diffuse edema apparent in the tissues of the cerebrum. Most of the ganglion cells show swelling, and there is a general chromotolysis. Occasional cells show an increased coloration, selecting a diffuse nuclear dye, together with a shrinkage of the cells. The perivascular lymph spaces are quite universally distended."

The symptoms produced in these two experiments are quite similar to those manifested in the case under study. The lesions found are apparently the result of the abnormal saturation of the tissues with salt and a resulting visceral edema following the abstraction of excessive quantities of fluid from the circulating media. The blood was scanty throughout, due evidently to abstraction of its fluids to satisfy the hypersaline tonicity of the tissues; nevertheless, in even favorable sections pronounced red cell deformity or excessive crenation of the red cells was not seen, indicating, apparently, that as yet the salt content of the blood did not balance that of the tissues, a condition quite in accord with previous experiments where the saline had been introduced into the intestinal canal.

Although the proportion of salt given, to body weight, was probably proportionately greater in the animals than in the case reported,

I think but little doubt can be entertained but that lesions akin to those in the experimental animals were present, and that death was induced as a result of them.

I was personally much impressed with the fact that no inflammatory changes developed in the kidneys as a result of excretion of so concentrated a fluid, for careful chemical examinations of the urine by Dr. Kaplan showed a constantly increasing excretion of NaCl. This certainly indicates in the animals, as also in the patient, that death was not due to inadequate capacity on the part of the kidneys to excrete the excessive salt, but points rather to insufficiency of liquid present in the body to both satisfy the salt and to still maintain the blood in a normally fluid state for the maintenance of the vital tissues in a physiological condition.

Certain apparent discrepancies exist in the varying tissues studied in the two experimental animals. Thus, in each some viscera were found edematous; others, even abnormally dry, and in the two practically similar experiments the lesions were not comparably constant. This I believe to be satisfactorily explained by the fact that death occurred soon after the administration of the salt and before the osmotic pressures had time to become balanced, and until this has taken place, according to Cushny, a continuous variation in the osmotic flow must take place.

In order that some idea might be gained as to the action of protracted excessive doses of sodium chloride, especially on the kidneys, the following experiments were made:

An adult rabbit, weighing 4 pounds 4 ounces, was selected. Two grams NaCl, in 10 c.c. of water, was administered on alternate days for thirteen times. After a rest of seven days, 5 grams, in 20 c.c. of water, was given, and, similarly, five days later, 6 grams. Twelve days later, 7 grams were administered, and again after two days, 7 grams, soon after which the animal died, giving an acute symptom picture similar, except in a much milder degree, to that seen in the former experiments. In all, 72 grams of NaCl were thus given in space of eighty-five days. The saline was given in each instance dissolved in a sufficient bulk of water, the idea being to avoid the local escarotic action of the concentrated saline on the gastric mucosa. The initial dose and each succeeding increased dose was

followed by the appearance of symptoms like those manifested in the acute poisoning, but of much less intense degree and of lesser duration. Where the doses were given on alternate days the symptoms became progressively less marked as the dose was continued.

The animal showed, from the first, very rapid emaciation, although it was abundantly fed throughout. Frequent examinations of the urine showed the rapid excretion of the chloride without the appearance of sugar, albumin, or other evidence of renal disease.

The autopsy showed no gross changes except for the presence of a gelatinous exudate in the intestine. No scarred areas were demonstrable in the gastric mucosa, and no gross lesions of the other viscera, except for the edematous appearance of the brain, liver, and heart. The skeletal muscles showed a strikingly dry appearance.

Microscopic examination of the kidney showed a swelling and granular alteration in the cells of the collecting tubes. There was no change apparent in the interstitial tissue or in the glomeruli. The bloodvessels were distended with blood and in places minute extravasations had taken place. The renal lesions were therefore apparently entirely of an acute type.

The liver showed very little change. Some of the cells appeared swollen and slightly edematous, a few somewhat disintegrated, and the interstitial tissue seemed to show in places a more than normal infiltration with lymphocytes. The bloodvessels were naturally filled with blood, but no other change was obvious.

No changes could be made out in the heart muscle. The lung was normal except for occasional areas of edema. The stomach showed occasional small areas of necrosis affecting the superficial portions of the mucosa only.

The brain showed in places a marked accumulation of small round cells about the smaller arterioles. There was an almost universal dilatation of the perivascular lymph spaces, but no changes could be made out in the ganglion cells.

This last experiment was repeated, with practically identical results, beginning with 1 gram of salt daily, finally terminating with 7 grams of concentrated saline, which caused death; whereas 7 grams, previously given in a greater dilution, failed to cause other than temporary disturbance.

Conclusions. Substantially the symptoms occurring in Dr. Bivings' case have been reproduced in the acute saline poisoning of the rabbits. From the lesions, as well as from the symptoms which developed in both the woman and the animals, it seems certain that the symptoms were largely due to the concentration of the saline rather than entirely from the amount of salt actually taken into the body. Even in these extreme examples the excretion of the excess salt was rapidly brought about and that without producing either symptoms or lesions of a very grave nature in so far as the kidneys alone are concerned.

From this brief study there seems to be no doubt but that the deleterious action of the salt lies in the fact that fluid is rapidly abstracted from the blood both for excretion and in effecting local edema, especially of the larger solid viscera. This is followed by a consequent concentration of the blood, the most serious results of which appear to follow from the lessened supply of the ganglion cells.

In so far as this study goes, the older theory that NaCl acts only by osmotic disturbance seems to be substantiated.

A broad question opened up by this well recognized action of the concentrated salines is that of the importance of the fluidity of the blood in many diseased conditions, especially such as in some forms of typhoid or dysentery, where the frequent intestinal discharges so diminish the fluid of the blood as to cause symptoms of a similar nature to develop.

Most of us have from time to time observed the same class of symptoms in patients after the saline cathartics, especially those of concentrated form, have been persistently given, and it seems very wise to bear this action in mind in the management of cases in which concentration of the body fluids may occur.

The failure of the NaCl, used medicinally or dietically, to produce renal changes other than such as evidently occur only as a result of the local edema and disturbed osmosis, would apparently indicate that in all probability the bad results which the chlorides produce in certain types of nephritis are due, not so much to an irritant or toxic action of the salt on the kidney tissue, as to its effect on the fluidity of the blood and on osmotic alterations.

DISCUSSION.

Dr. S. J. Meltzer: I should like to ask Dr. Brooks how large a quantity of saline solution was injected.

Dr. Brooks: Nine ounces. In rabbits, 5 grams were sufficient to cause death inside of one hour if it was sufficiently concentrated.

Dr. Meltzer: I had a similar experience many years ago, and the only effect was that there occurred a hemorrhage from the rectum. In experiments which Dr. Joseph and I carried out on dogs it was found that 60 to 70 c.c. per kilo of a 6 per cent. solution of sodium chloride had to be injected intravenously before a fatal issue took place.

Dr. Brooks: When a saturated solution of sodium chloride is rapidly introduced into the intestinal tract, more disastrous results follow than if the same amount is introduced slowly directly into the circulation, as has been indicated by our experiments.

THE TREATMENT OF ANEURYSM OF THE AORTA BY THE INTRODUCTION OF WIRE AND THE PASSAGE OF A GALVANIC CURRENT.

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Aneurysm of the aorta is essentially a fatal disorder sooner or later, partly on account of the resulting interference with the blood-distribution and pressure-phenomena, but largely and inherently because of the underlying degenerative state of the vessel-wall, so that if correction or repair be effected in one situation, active manifestations are likely to appear in another situation. The affection is almost invariably associated with more or less wide-spread atheroma of the arterial system, and antecedent syphilis appears to be far and away the commonest cause. The dilatation or diverticulation of the bloodvessel must, accordingly, be looked upon merely as a local expression of changes widely distributed throughout the vascular system, and accordingly the results of any therapeutic procedure can at best be only palliative, except in the small group of cases in which the lesion arises from purely local influences, such as traumatism or adjacent disease. Nevertheless, it will not be gainsaid that measures of temporary relief are often indicated, either for the amelioration of symptoms or for the prolongation of life. In this connection the fact should not be ignored that under certain conditions life may be continued for many years in the presence of an aneurysm and also that a sacculated aneurysm of the aorta may, and occasionally does, undergo spontaneous cure by the total occlusion of the aneurysmal sac by fibrous laminated adherent clot, and be discovered at autopsy only as an incidental phenomenon.

Furthermore, it is impossible to foresee the outcome of the brilliant experimental work that has been done and is being continued in the plastic surgery of the vascular system. Nevertheless, there will remain cases in which symptomatic treatment only will be possible.

In the treatment of aneurysm of peripheral vessels, with abundant anastomotic connections, deligation, with or without excision or resection of the aneurysmal sac, has yielded satisfactory and at times, even brilliant results, but this mode of procedure is scarcely applicable to aneurysm of the aorta, and, more particularly its thoracic division, partly on account of anatomic limitations with respect to the establishment of a collateral circulation, and partly by reason of the practical inaccessibility of the disease-focus. Various modes of treatment, dietetic, medicinal, physical, have been applied to aneurysms of the latter class, with varying measure of success. Among the most rational and most useful of these may be mentioned rest, restricted diet, ergot, iodides, calcium chloride, adrenalin, introduction of foreign bodies, electricity. Of foreign bodies there have been introduced into the aneurysmal sac substances such as horsehair, catgut, silk, watchspring, needles, and wire of various kind.

Charles H. Moore and Charles Murchison[1] first employed fine iron wire in this manner, introducing twenty-six yards through a cannula into an aneurysm of the thoracic aorta. The tumor was at first reduced in size, but subsequently it became larger, and the patient died on the fifth day. Postmortem examination disclosed abscess of the left kidney and pericarditis.

The possibility of treating aneurysm by transfixion with needles occurred to Velpeau[2] and to Benjamin Phillips;[3] while Ciniselli[4] recommended galvano-puncture or electrolysis by means of needles introduced into the aneurysmal sac.

Burresi and Corradi[5] introduced 42 cm. of No. 30 annealed wire through a cannulated needle into the sac of a large aneurysm of the

[1] Medico-Chirurgical Transactions, 1864, xlvii, 129.

[2] Mémoires de l'Académie des Sciences, December, 1830.

[3] Medical Gazette, 1831, 499; also pamphlet, A Series of Experiments for the Purpose of Showing that Arteries may be Obliterated without Ligature, Compression, or the Knife, 1832.

[4] Gazette des Hôpitaux, 1868.

[5] Lo Sperimentale, April, 1879, p. 445.

ascending division of the arch of the aorta, and passed a constant current. Temporary improvement ensued, but death took place three and a quarter months after the operation. This latter procedure variously modified has since been carried out in a moderate number of cases—of which I have been able to tabulate 38—and the results appear to justify its employment under suitable conditions. It is applicable only to sacculated and not to fusiform aneurysms, particularly if lesser measures have failed, and even and perhaps especially when alarming symptoms are present or rupture is threatened. The most that can be hoped for under such circumstances is amelioration of symptoms and prolongation of life, and these ends have been attained in most instances in which the procedure has been employed. In isolated instances the inevitable fatal issue appears to have been hastened, but in the vast majority the intervention has been justified by the results.

The technique of the procedure is extremely simple. Under aseptic conditions a hollow needle of gold, silver or platinum, insulated except at its tip, is introduced to a considerable distance into the most prominent part of the aneurysmal sac; care being taken to avoid puncture of the remote opposite side of the vessel wall. Through the needle gold or silver wire is fed in amount sufficient loosely to fill the sac. Ordinarily ten or twelve feet of wire will be sufficient. Should the wire kink before the desired amount is introduced, the needle may be withdrawn and introduced in another situation, or a second needle may be introduced, and wire insinuated through it. Indeed, several needles may be introduced at the same sitting. The end or ends of wire are connected with the positive pole of a galvanic battery and a current gradually increased to 60, 80, or 100 milliamperes, and as gradually decreased, is passed over a period of from an hour to an hour and a half. The negative pole of the battery is placed upon some indifferent point, as upon the back. A spurt of blood usually follows introduction of the needle, but the hemorrhage is not considerable and it soon ceases. Pulsation may begin to subside during the introduction of the wire, but as a rule, this effect does not appear until the passage of the current, and at the same time the patient often expresses relief from distressing symptoms, such as pain and dyspnœa. In many instances

the improvement is progressive and persists for a varying period of time, and in one case it was maintained for nearly twelve years. The operation is remarkably free from accident or complication, transient hemiplegia having been exceptionally observed. Death may result from hemorrhage or the effects of pressure and exhaustion or from rupture of a second aneurysm, and at times from an entirely unrelated cause. Only sacculated and not fusiform aneurysms are suitable for the operation. Experience and experiment have shown that gold or silver wire is the best to employ, the latter having the advantage of lesser cost. The positive pole is preferred for connection with the wire on account of the firmer clot produced at this pole.

In addition to the recorded cases I am able to report two that have recently been under my observation.

Case I.—A sheetmetal worker, aged sixty-four years, was admitted to the Philadelphia General Hospital March 26, 1909, complaining of dyspnœa, pain on both sides of the chest, cough, expectoration, headache. The dyspnœa has been present for a year, and had become worse six weeks previously. At this time the pain in the chest appeared, and a cough of long standing became aggravated. The man had worked at his trade until four weeks before admission to the hospital, when he was compelled to give up on account of the difficulty in breathing. Physical examination disclosed the signs of effusion into the left pleural cavity, and on aspiration about three pints of clear serous fluid were evacuated. The apex-beat of the heart, which previously had been one and a half inches to the right of the sternum, receded to the left of the sternum. The normal heart-sounds were replaced by murmurs, but little transmitted. The voice was hoarse, and there was a metallic cough. Bulging, with pulsation, was visible on the upper anterior aspect of the left chest, with dulness on percussion and a to-and-fro murmur on auscultation. Tracheal tugging was distinct. The percussion note over the greater part of the left chest was dull, with diminished vocal resonance and fremitus, and friction sounds toward the base. Over both lungs bubbling rales were audible. On laryngoscopic examination the left vocal band was found immobile. The urine was free from albumin and sugar. *X*-ray examination disclosed an aneurysm of the aorta.

As the swelling and the pulsation of the left chest increased and the general symptoms grew worse the proposition was made to the patinet that wire be introduced into the sac and a galvanic current be passed, and in this he acquiesced. Accordingly on April 24, 1909, after injecting ¼ gr. morphine hypodermically, and inducing local anesthesia with cocaine, Dr. Ralph S. Lavenson introduced at the most prominent point an insulated hollow gold needle in the second interspace just to the left of the sternum. A small amount of dark, thick blood oozed from the needle. About twelve feet of gold wire was introduced into the sac, blood meanwhile flowing more freely. The end of the wire was connected with the positive pole of a galvanic battery, while a large wet pad connected with the negative pole was applied to the back. The curent was started at 5 milliampéres and thus continued for three minutes, being increased 5 milliampéres every succeeding three minutes until a total of 60 milliampéres was reached. It was maintained at this level for ten minutes, and then gradually reduced 10 milliampères every three minutes. Fifty-eight minutes were consumed in the passage. During its progress pulsation diminished. The patient withstood the operation well and made no complaint of pain. Subsequently there was temporary return of the pain on both sides of the chest. For a time also a tender swelling made its appearance at the site of puncture, but this soon subsided. The patient, however, failed to gather strength, and troublesome cough persisted, and without the development of other symptoms death took place from exhaustion on May 22, 1909, four weeks after the operation.

There was some delay in securing an autopsy, and this was not held until five days after death. The body had been embalmed and and was in a good state of preservation. The right lung was bound by moderate adhesions, which were readily detached. The left lung was held by more numerous and firmer adhesions and it was greatly compressed. The anterior mediastinum was occupied by the heart and a large, firm mass. The heart was in a somewhat transverse position, the right auricle being situated to the right and the right ventricle to the left, while the left auricle and ventricle were altogether posterior. The pericardial cavity was obliterated by adhesions. The ascending and transverse portions of the arch of

the aorta were the seat of an immense aneurysm as large as a child's head, and almost entirely filled with clot which in places had undergone fibrous transformation, and in the midst of which was a coil of gold wire. The descending portion of the arch and the thoracic aorta were the seat of marked atheroma, with calcareous deposits. The liver was large, hard and cirrhotic. The kidneys were large and cyanotic, with parenchymatous and interstitial changes. The spleen was soft and voluminous. The lungs were firm and on section frothy.

Case II.—V. M., an Italian laborer, aged fifty-nine years, was admitted to the Philadelphia General Hospital, September 10, 1908, complaining of precordial pain, cough, expectoration, dyspnœa and weakness. He had been a saloonkeeper for thirty-two years and had indulged in alcohol to excess. He had suffered from several of the diseases of childhood, from smallpox at six, and he had had an attack of gonorrhœa at twenty, and a chancre at thirty. For eight months he had been complaining of pain in the precordium, progressive in severity, radiating in the course of the great vessels and extending down the left arm, together with cough and expectoration. The pulse was small, slow and thready, the right smaller and slower than the left. Pulsation was visible in the vessels of the neck. The chest was barrel-shaped and presented a pulsating swelling to the left of the sternum between the second and fourth intercostal spaces, and yielding dulness on percussion. No thrill was palpable, but a bruit was audible on auscultation. The action of the heart was deliberate, rhythmic, and forcible; the first sound was clear, the second accentuated at the base. The pupils were moderately dilated, but they reacted to light and in accommodation. The urine was free from albumin and sugar. Skiagraphic examination disclosed an aneurysm of the arch of the aorta. On September 28, fourteen feet of gold wire was introduced by Dr. Ralph S. Lavenson into the pulsating mass, and a galvanic current was passed. The current strength was begun at 5 milliampéres and was gradually increased to 75 milliampéres and as gradually reduced. The patient was somewhat restless during the course of the procedure, and he coughed slightly with each increase in the strength of the current. Relief was afforded by a hypodermic injection of morphine, gr. $\frac{1}{4}$,

and the patient slept for a portion of the time. Pulsation soon diminished and became almost imperceptible. Pain, however, persisted and at a later date pulsation returned. On May 1, 1909, the patient went to visit friends, and he returned on May 5 with a pulsating mass of increased size at the site of the earlier swelling. Death took place suddenly on May 6, seven and one-fourth months after the operation.

On postmortem examination a globular swelling was visible upon the anterior aspect of the left side of the chest between the second and fifth ribs and the median and nipple lines, and the centre of which exhibited a dark-red discoloration. The underlying third rib was fractured. The right pleural cavity was free and the right lung was covered at its apex by a small area of thickened pleura, but it was in other respects normal. The left pleural cavity contained 200 c.c. of slightly cloudy, straw-colored fluid, in which floated flakes of fibrin. The pleural surfaces were moist and glistening. The left lung was pale gray in color and crepitant throughout. On section a considerable amount of frothy fluid escaped. The pericardial cavity contained a large amount of currant-jelly clot under such pressure that it was forcibly extruded when the pericardium was incised. The heart was flabby and covered by a considerable amount of epicardial fat. The myocardium was pale and cloudy. All of the chambers of the heart were dilated, but the walls were not hypertrophied. The valves and orifices presented no abnormality. The aorta was extremely atheromatous, the intima in places being punctured and fissured. The ascending and transverse portions of the arch of the aorta were greatly dilated and from the anterior aspect of the latter bulged a large sacculated aneurysm measuring 8 x 6 cm. The sac was largely filled by organized thrombus and recent blood-clot in the midst of which loosely coiled lay 350 cm. of fine gold wire. The overlying third rib was partially eroded and fractured, and the aneurysm was adherent to the second and fourth ribs. A short distance above the aortic cusps the vessel wall was softened and eroded, and it was at this point that the fatal hemorrhage into the pericardium had taken place. Several other weakened spots in the wall with beginning bulging were visible in other parts of the aorta. The

spleen was considerably enlarged. It was friable and it tore in removal. Its structure was pale, the capsule presenting a variegated appearance, with dark and red spots. The kidneys were pale and flabby, the capsule stripping easily and leaving a smooth surface behind. On section they presented a cloudy appearance, the cortex being slightly increased in thickness and pale in color. The right kidney was smaller than the left. The liver was enlarged and measured 20 x 18 x 9 cm. It was pale and flabby and its capsule was smooth. Section presented a dirty yellow appearance; the acini were not visible.

The following table comprises 34 cases that I have been able to collect from the literature, together with two cases recently reported by Beardsley, Rhoads, and Saurman before the College of Physicians of Philadelphia, February 3, 1910, and the two cases of my own.

In addition Hunner[1] refers to a case of Dr. John Neff, of Baltimore, in which operation was performed on three occasions by D. D. Stewart, of Philadelphia, and apparently not otherwise reported. The patient was a traveling salesman, with a large thoracic aneurysm. Ten feet of wire was introduced February 5, ten feet April 1, and five feet June 5. Death took place from rupture and hemorrhage November 17.

Dr. Robert N. Willson, Jr., of Philadelphia, informs me that he has treated 3 cases of aneurysm of the ascending portion of the arch of the aorta and 1 case of aneurysm of the descending portion by the introduction of 15 feet of gold wire and the passage, throughout an hour, of a galvanic current gradually increased to 160 milliampères and then gradually diminished. In three of the patients death appeared imminent, and although they were helped symptomatically, life was prolonged but a few days. One had been wired twice previously without advantage, and the patient was able to return to work after the third operation, and was still living at the date of Dr. Wilson's letter to me.

[1] Loc. cit.

Reporter.	Sex.	Age.	Situation.	Operation.	Result.	Remarks.
Burresi-Corradi, Lo Sperimentale, April, 1879, 445	M	43	Ascending arch	42 centimeters No. 30 annealed wire; 16 cells, 25 minutes	Death, three and one-quarter months	
Richard Barwell, Lancet, June 5, 1886, 1058	M	39	Descending arch	10 feet finest steel wire; 9 to 10 milliampères, 70 minutes	Death, seven days	Exhaustion; rupture of second sac
J. W. Roosevelt, Medical News, 1887, 397	M	25	Arch	225 feet fine steel wire (oo); 25 milliampères, 30 minutes	Death, twenty-third day	Gangrene toe
Robert Abbe, Medical News, 1887, 397	M	46	Subclavian	100 feet No. 1 catgut; 8 days later 150 feet fine steel wire; 50 to 100 milliampères, 70 minutes	Death, second day	Current reversed; dissecting; rupture into trachea
W. W. Kerr, Occidental Medical Times, January, 1889, 1	M	38	Ascending arch	6 feet drawn silver wire; 50 minutes	Death, eighteenth day	Fusiform
W. W. Kerr, Occidental Medical Times, January, 1889, 1	M	56	Ascending arch	Galvano-puncture; later 10 feet wire, 30 minutes	Working as a pavior three years after operation*	Fusiform
Julius Rosenstirn, Amer. Jour. Med. Sci., 1891, ci, 55	M	25	Ascending arch	Galvano-puncture; later 26 feet silver wire, 30 minutes	Death, eleven years and eight months*	
D. D. Stewart, Trans. College of Physicians of Philadelphia, 1892, xiv, 68	M	30	Thoracic and abdominal	Heavy silver wire; 70 milliamperes, 1 hour	Death, ninth day	Rupture
E. P. Hershey, Therap. Gaz., 1896, 590	M		Innominate	2½ feet No. 28 gold wire; 70 milliampères, 45 minutes	Death, fourteen months	
D. D. Stewart and J. L. Salinger, Amer. Jour. Med. Sci., 1896, cxii, 171				10 feet No. 30 gold wire; 30 to 80 milliampères, 75 minutes	Death, three and one-half years	Death from cerebral thrombosis
D. D. Stewart, Trans. College of Physicians of Philadelphia, 1897, xix, 38	M	40	Innominate			
W. H. Noble, Phila. Med. Journal, June 25, 1898, 1203	M	37	Abdominal	8½ feet No. 30 gold wire; 70 milliampères, 37 minutes	Death, eight months	Abdominal section; death not due to aneurysm
H. A. Hare, Therap. Gaz., 1898, 293; 1900, 9; Penna. Med. Journal, 1898-1899, 312	M	46	Transverse and descending arch	9 feet fine gold wire, 80 minutes	Death, seven months	Death from exhaustion; second aneurysm distal
D. D. Stewart, Phila. Med. Journal, Nov. 12, 1898, 1011	M	40	Splenic	10 feet silver wire; 50 milliampères, 30 minutes	Death, fifth day	Abdominal section
D. D. Stewart, Phila. Med. Journal, Nov. 12, 1898, 1011	M	42	Thoracic	14 feet fine gold wire; up to 80 milliampères, 80 minutes	Death, fifth day	Life prolonged; comfort afforded
J. C. Reeve, Annals of Surgery, 1899, xxx, 704	M	49	Abdominal	7 feet silverplated, soft copper wire; 80 milliampères, 50 minutes	Death, twenty-four hours	Abdominal section; strand of wire extended to aortic valves
E. S. Corson, Phila. Med. Journal, March 4, 1899, 511	M	31	Ascending arch	6 feet drawn silver wire; 8 dry cells, 2 hours	Death, forty-two hours	Death from arrest of respiration
H. A. Hare, Therap. Gazette, 1900, 9	M	48	Arch	10 feet gold wire; 1 month later 10 feet gold wire in each of two places; 10 to 100 milliampères, 90 minutes	Death, eight months	Life prolonged
H. A. Hare, Therap. Gazette, 1900, 510				10 feet gold wire; 5 days later 10 feet gold wire; up to 85 milliampères, 1 hour	Death, sixth day	Death from respiratory failure
G. L. Hunner, Bulletin Johns Hopkins Hospital, Nov. 1900, 263	M	27	Abdominal	No. 27 undrawn silver wire; kinked; withdrawn; 12 minutes; second wire, 17 inches; third wire, 38 inches; 30 to 100 milliampères, 85 minutes	Death, forty hours	Abdominal section; symptoms of internal hemorrhage; death probably hastened

G. L. Hunner, Bulletin Johns Hopkins Hospital, Nov. 1900, 263	M	25	Abdominal superior mesenteric	5 feet silver wire (copper alloy); 30 to 70 milliampères, 80 minutes	Death, twentieth day	Abdominal section; death from hemorrhage
G. L. Hunner, Bulletin Johns Hopkins Hospital, Nov. 1900, 263	M	51	Thoracic	10 feet silver wire (copper alloy); 10 to 20 milliampères, 75 minutes	Death, six months	
G. L. Hunner, Bulletin Johns Hopkins Hospital, Nov. 1900, 263	M	39	Thoracic	10 feet silver (copper) wire; 10 milliampères, 1 hour; after 24 days, 10 feet silver (copper) wire; 10 milliampères, 1 hour	Death, eleven weeks	Death from compression of trachea
G. L. Hunner, Bulletin Johns Hopkins Hospital, Nov. 1900, 263	M	30	Abdominal	8 to 9 feet higdly drawn sterling silver wire; 10 milliampères, 1 hour	Death, fifth year*	Fusiform aneurysm; abdominal section
H A. Hare, Therapeutic Gaz., 1903, 19	M		Thoracic	9 feet gold wire; second operation 6 months later	Death shortly	Repeated copious hemorrhage
J. Daland, Penna. Med. Journal, 1903-1904, 134	M	52	Left subclavian	20 feet gold wire; 1 to 80 milliampères, 110 minutes	Death, twentieth day	Thrombosis of carotid artery from pressure of aneurysm
Raymond Russ, Occidental Medical Times, 1903, 284	M	50	Transverse arch	1 foot No. 26 soft silver wire; 50 to 100 milliampères, 55 minutes; 15 days later, 6 feet No. 22 silver wire; 50 to 60 milliampères, 40 minutes	Death, five weeks	Pressure on trachea
J. L. Salinger, Therapeutic Gazette, 1903, 438	M	73	Ascending arch	16 feet wire; 5 to 65 milliampères, 75 minutes	Death, five months	Transitory hemiplegia and aphasia on third day; death from pneumonia
R. C. B. Maunsell, British Med. Journal, June 18, 1904, 1421	M	28	Abdominal (celiac axis)	6 yards No. 28 silver wire; 1 to 65 milliampères, 30 minutes	Death, forty-seven days	Abdominal section; hemorrhage
H. A. Ballance, Lancet, Oct. 1, 1904, 939	M	44	Ascending arch	8 feet No. 9 silver wire; 24 to 42 milliampères, 45 minutes	Death, ten months	Great relief of symptoms; old emboli kidneys; recent infarct lung
H. A. Hare, Therapeutic Gazette, July, 1905, 433	F	50	Transverse arch	8 feet gold wire; 5 to 50 milliampères, 30 minutes	Death, six months	
H. A. Hare, Therapeutic Gazette, July, 1905, 433	M	42	Innominate	2 feet gold wire; 5 to 30 milliampères, 40 minutes	Death, two months	Exhaustion; interference with respiration and deglutition; no trace of wire at autopsy
H. A. Hare, Therapeutic Gazette, July, 1905, 433			Thoracic	9 feet gold wire; 5 to 50 milliampères, 45 minutes	Death, four months	Pressure; exhaustion
Gaston Torrance, Alabama Med. Journal, 1905-6, xviii, 487	M	40	Descending arch	5 to 6 feet No. 27 drawn silver wire; 10 to 20 milliampères, 1 hour	Death, three and one-half weeks	Hemorrhage; rupture into œsophagus
C. A. Griffiths, Lancet, Aug. 12, 1905, 442	M	37	Abdominal	1 foot fine silver wire; kinked; more wire (6 feet); 15 to 25 milliampères, 15 minutes	Death, five and one-half hours	Abdominal section; double loop of wire had passed into aorta two inches; wire connected with negative pole
E. J. G. Beardsley, Samuel Rhoads, J. Shelley Saurman*	M	57	Descending arch	32 feet No. 26 gold wire; 5 to 60 milliampères, gradually increased and decreased	Comfortable after four months	
E. J. G. Beardsley, Samuel Rhoads, J. Shelley Saurman*	M	37	Ascending arch	18 feet No. 26 gold wire; 5 to 60 milliampères, gradually increased and decreased	Death, three weeks	Death from rupture of aneurysm fusiform
A. A. Eshner	M	64	Ascending and transverse arch	12 feet gold wire; after 8 weeks 10 feet gold wire; 5 to 50 milliampères, 58 minutes	Death, four weeks	Death from exhaustion
A. A. Eshner	M	59	Ascending arch	14 feet gold wire; 5 to 75 milliampères	Death, seven and one-quarter months	Rupture into pericardium

* Personal communication.

Of the 38 cases included in the table that I have prepared, 36 occurred in males, 1 in a female, and in 1 the sex was not mentioned. The age of the patient was mentioned in 35: Five were between twenty-five and thirty, 3 between thirty and thirty-four, 6 between thirty-five and thirty-nine, 7 between forty and forty-four, 4 between forty-five and forty-nine, 4 between fifty and fifty-four, 4 between fifty-five and fifty-nine, 1 was sixty-four and 1 was seventy-three. The arch of the aorta was the seat of the aneurysm in 18 cases (ascending portion in 9, descending portion in 3, "arch" in 2, transverse portion in 2, ascending and transverse portions in 1, transverse and descending portions in 1), the thoracic aorta in 5, the abdominal aorta in 5, the innominate artery in 3, the subclavian artery in 2, the superior mesenteric artery in 2, the thoracic and abdominal aorta in 1, the splenic artery in 1, and the celiac axis in 1. Gold wire was used in 16 of the cases, silver wire in 15, steel wire in 4, and silver-plated copper wire in 1. The duration of life following the operation was as follows: Five and one-half hours in 1, twenty-four hours in 1, forty hours in 1, forty-two hours in 1, two days in 1, five days in 1, six days in 1, seven days in 1, nine days in 1, eighteen days in 1, twenty days in 2, three weeks in 1, twenty-three days in 1, three and one-half weeks in 1, four weeks in 1, five weeks in 1, forty-seven days in 1, two months in 1, eleven weeks in 1, three and one-fourth months in 1, four months in 1, five months in 1, six months in 2, seven months in 1, seven and one-fourth months in 1, eight months in 2, eight and one-half months in 1, ten months in 1, fourteen months in 1, three and one-half years in 1, five years in 1, eleven years and eight months in 1. One patient was living three years after the operation, but his subsequent history is unknown. (Kerr, loc cit.)

Conclusions. Aneurysm of the aorta is essentially a fatal disorder, although exceptionally spontaneous cure takes place. Accordingly, treatment can, as a rule, be only palliative, relieving symptoms and prolonging life. Deligation is inapplicable from anatomic considerations. Rest, ergot, iodides, gelatin, calcium chloride, adrenaline chloride and introduction of foreign substances, with or without the passage of a galvanic current, have been employed. Horsehair, catgut, needles, watchspring and wire of various kind

have been introduced, with varying result, and a galvanic current has been passed through conducting substances. Wiring with electrolysis has been employed in a moderate number of instances, with satisfactory results in the majority. The procedure has proved simple and safe, but it is applicable only to sacculated and not to fusiform aneurysms.

DILATATION OF THE AORTA.

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Introduction. As regards the subject of this paper, there is some difficulty in terminology, as the term dilatation of the aorta is variously applied. In this connection it is used to describe the condition in which the aorta is enlarged in its whole circumference, the extent of this varying sometimes being of the whole arch, sometimes extending to the point where the aorta passes through the diaphragm, and sometimes involving the whole course of the aorta. Is it proper to consider such a condition as an aneurysm? This will depend on the meaning we attach to the term. If we use it in the widest sense as being properly applied to any increase in the size of an artery, this diffuse dilatation would be included. On the contrary, if the term aneurysm be restricted to a tumor containing blood in direct communication with the cavity of the heart or the lumen of an artery, the diffuse dilatation is excluded. The fusiform or globular dilatations of the aorta were designated "true" aneurysms by the older writers. Thoma described them under the designation of aneurysma verum diffusum, and Walshe as peripheric dilating aneurysms. The terms true and false as applied to aneurysms have been used in a confusing way, having been employed in exactly opposite significations. Scarpa used the term "true" to designate aneurysms in which all the coats were not present, and "false" to describe those in which all the coats remained and no coagulation had occurred, but the terms were subsequently applied in exactly an opposite sense. It is evident that such distinctions are of no definite value, and the terms false and true are better dropped from the terminology.

In this article the term dilatation is employed to designate a condition which, strictly speaking, probably comes under the term aneurysm as we generally use it, but there is no question that in its clinical aspect it differs considerably both from the saccular and ordinary fusiform aneurysm of the aorta. As Gairdner pointed out, in these cases of diffuse dilatation of the aorta there is nothing that, "clinically speaking, can be definitely called a tumor."

It is surprising how little attention has been given to diffuse dilatation of the aorta, although it has long been recognized. In some text-books it is referred to under the headings of chronic aortitis and aneurysm. Morgagni distinguished between the enlargement which involved the whole circumference of the aorta and that which rose from one part, while Scarpa did not regard the enlargement of the whole aorta as aneurysm. Vieussens and Boerhaave also recognized the condition, but it is not always easy to make out whether they are describing a large fusiform aneurysm or the diffuse dilatation.

The first accurate description was given by Joseph Hodgson[1] in 1815, who distinguished the condition from ordinary aneurysm and referred to it as a "preternatural permanent enlargement of the cavity of an artery." By many French writers the condition is termed *maladie de Hodgson*, although some regard an associated aortic insufficiency as an essential part of the picture. Thoma,[2] in 1888, wrote extensively of this form, and gave one of the best descriptions of it. As Osler points out, it is a striking commentary on the difficulty of recognition that, of the cases studied by Thoma, very few had been recognized clinically. It is one of the conditions which has heretofore been more often found in the dead house than recognized in the wards. This is due to various reasons: the condition itself may not give any symptoms, and its signs are overlooked; or signs suggesting some other disease, especially angina pectoris, may cause error; or the signs of associated cardiac disease may dominate the picture.

For this study a series of sixty cases is considered, all of which occurred in the wards of the Johns Hopkins Hospital or were seen in consultation.

[1] Diseases of Arteries and Veins, London, 1815.
[2] Virchow's Archiv, 1888, cxi, 76; 1888, cxii, 259, 383; 1888, cxiii, 244, 505.

Etiology. There are probably two main groups, one in which the dilatation occurs with an acute infectious disease, notably rheumatic fever, and the second in which the factors are essentially those which cause arteriosclerosis and aneurysm. In the latter group the essential factor appears to be disease of the vessel wall, with loss of elasticity and subsequent dilatation, probably largely in the nature of a mechanical process. The various factors in this series are as follows:

1. *Age.* Eleven to twenty years, 1; twenty-one to thirty years, 1; thirty-one to forty years, 16; forty-one to fifty years, 16; fifty-one to sixty years, 16; sixty-one to seventy years, 8; seventy-one to eighty years, 2.

Of the 18 patients under the age of forty years, 15 were males (9 white and 6 colored) and 3 females (1 white and 2 colored). The relative preponderance of colored patients among the younger ones is a striking commentary on their tendency to early vascular degeneration. The majority of these 18 patients gave a history of severe muscular exertion for many years; there was a definite history of syphilis in 6 of them, and 7 had aortic insufficiency, while in 5 of the last 10 cases there was a history of heavy drinking. It will be noted that the number is the same in the fourth, fifth, and sixth decades. In regard to the small number in later periods it must be kept in mind that these figures come from a general hospital, and that those with diffuse dilatation in later life rarely have any symptoms from it. It occurs not uncommonly without any symptoms in the aged in almshouses and asylums, and is only recognized at autopsy.

2. *Sex.* The condition occurs most often in males, as might be expected. In this series there were 54 males and 6 females, 4 of the latter being colored.

3. *Color.* The colored race shows a relatively high proportion; of this series, 39 were white and 21 colored (the total medical admissions being about 5 to 1). This is in agreement with the relatively high incidence of aneurysm and sclerotic vascular disease among them, due probably to alcohol, syphilis, and hard work. The total medical patients with aneurysm numbered 399 (white 239, colored 160), so that the relative proportions for aneurysm and dilatation of the aorta are about the same.

4. *Syphilis.* This stands out as an important cause, but probably not so markedly as in aneurysm. There are two principal forms of dilatation influenced by syphilis, one in which the process occurs with an acute syphilitic aortitis, usually seen in young adults, and the other in which the condition results from general chronic changes in the vessel wall. In this series there was a definite history of syphilis in 17 cases and probable in 8 cases. The Wassermann reaction was tried in 8 cases, with a positive result in only 3 cases. This is in such striking contrast to the results in aneurysm that it suggests that syphilis does not play such an important etiological part in dilatation.

5. *Work and Muscular Exertion.* These are factors in dilatation exactly as they are in the production of general arteriosclerosis. Occupations which involve very severe exertion at irregular times, such as that of stevedore, will evidently favor the condition. A sudden increase in the blood pressure must have more influence on the aorta than on any other vessel. In this series 39 of the patients had done hard muscular work, 7 were engaged in business, and 7 did housework. The others had light occupations. Among those who had done hard work, in a large proportion this had involved severe sudden irregular exertion. This is very striking in going over the histories, and an unusual proportion of the men had occupations which involved the lifting of heavy weights.

6. *Alcohol.* How much this is a factor, it is difficult to say. In this series 25 had used alcohol to excess, and 22 were described as moderate users, which is certainly a high proportion.

7. *Acute Specific Infections.* These probably play a more important part than is generally considered, for when we remember how much damage may be done to the aorta in the course of an attack of typhoid fever, it seems probable to suppose that later changes may gradually develop, especially if other factors are added. Whether or not there is a true primary aortitis apart from syphilis is difficult to say, but it seems probable to suppose that it may occur. There is one infection in which dilatation may occur during the acute attack. This is rheumatic fever, in which there may be an acute dilatation of the aorta, usually with aortic endocarditis. There was a definite history of this disease in 13 cases, and in 6 others of an

attack of acute arthritis the nature of which was doubtful. A striking feature was the large proportion of the younger patients who gave a history of rheumatic fever, for of the 18 patients under the age of forty years, 9 had suffered from rheumatic fever, several with repeated attacks, which seems a high percentage. As the majority of these had aortic insufficiency, it is a reasonable supposition that acute aortitis occurred, which was followed by chronic changes. Even in young children dilatation of the aorta may occur with aortic endocarditis in rheumatic fever, and it seems reasonable to suppose that this is permanent in some cases. There was a history of typhoid fever in 8 cases, 3 of these being below the age of forty years. In one case, a man aged thirty-three years, the symptoms began during recovery from an attack of typhoid fever, but he had several attacks of rheumatic fever previously. The same condition may occur with acute sepsis. Some writers have suggested that there might be an extension of inflammation from an endocarditis, pericarditis, or pleuritis. It seems reasonable to suppose that if recovery followed an attack of acute aortitis, a chronic condition with tendency to dilatation would be left.

8. *Old Age.* This is only a cause in so far as the passage of years brings sclerotic changes. It is probably then only to be regarded as one of the natural changes.

9. *Malaria.* There are few conditions for which malaria is not given by some one as a causal factor. There does not seem to be any evidence to suggest any association with dilatation of the aorta, but it is constantly repeated by various authors.

10. *Severe Strain or Exposure.* The importance of a factor such as this is difficult to estimate, and any effect is probably only in causing symptoms to appear from a condition already present. There is one striking example in this series:

The patient, a white male, aged thirty-seven years, a ship captain, came complaining of shortness of breath. He had not had typhoid fever, rheumatic fever, or pneumonia. Although he had followed the sea most of his life, there was no history of syphilis, and he had used alcohol very moderately. His illness began one month before, previous to which he had been perfectly strong and well. His ship caught fire, and they had to take to the boats. Naturally he was under

a heavy mental strain, and in addition was exposed to bad weather before they were picked up, as a result of which he had a severe attack of bronchitis, with which there was shortness of breath, which continued. He had a well-marked dilatation of the aortic arch, seen with the fluoroscope, with dulness over the manubrium and in both the right and left first and second interspaces, where there was a faint visible pulsation. The heart was not enlarged; the sounds were clear, the second being very ringing. The pulse rate was normal, and there was moderate thickening of the peripheral vessels. His symptoms gradually cleared, and he has been well for some years.

11. *Trauma.* The influence of this is most probably shown in determining the onset of symptoms. In one patient, a miner, aged thirty-nine years, the onset of symptoms followed an injury sus-sustained by being struck on the chest by a dump cart in a mine. He was knocked unconscious and remained so for twenty minutes. On recovering consciousness he had dyspnœa and severe pain in in the chest, which became less after three weeks, but the dyspnœa continued. He was found to have aortic insufficiency, which was thought to have been due to rupture of an aortic cusp. He had been previously a very hard worker in a steel plant, where he carried heavy weights, had drunk heavily, and probably had syphilis, so that there were causal factors other than the trauma.

Morbid Anatomy. The lesions include those of chronic aortitis and secondly the dilatation. This is of varying extent, and may involve only a portion of the thoracic aorta or extend throughout the whole course of the thoracic and abdominal aorta. In the cases of this series coming to autopsy the process did not extend beyond the point where the aorta passes through the diaphragm. The dilatation may end here very abruptly; thus, in one case the aorta measured 8 cm. in circumference at the lower part of the dilatation, and only 4.5 cm. below. The form of the dilatation is various, and may be spindle, spheroid, or pyriform in shape, or sometimes like a flabby bag. The orifices and part of the vessels given off from the aorta may be involved in the dilatation.

Associated conditions may have a marked effect on the symptoms. Thus, if the chronic sclerotic process has involved the aortic ring,

there is likely to be aortic insufficiency in consequence of the valvular changes. If the first part of the aorta is specially involved there may be coronary artery disease. If the orifice of the left subclavian is narrowed the pulse in that arm may be small. One result is of special interest, namely, relative aortic insufficiency due to dilatation of the aortic ring. There were two such cases in this series. In one case a loud aortic diastolic murmur was heard for some time, which disappeared before death, and at autopsy the aortic valves were normal and apparently closed the orifice completely. Probably the decrease in blood pressure, for some days before death, allowed the dilatation of the aorta to diminish and the aortic ring returned to its usual size.

Thrombus formation in the dilated aorta is not common. Osler[1] mentions a specimen in the Museum of McGill University in which the descending thoracic and abdominal aorta was dilated and the abdominal aorta filled by a densely laminated thrombus. Although in the majority of cases the aorta shows marked gross evidences of disease, yet this is not always the case, and the intima may be smooth and apparently normal.

The association of sacculated aneurysm with dilatation of the aorta is mentioned, but no instance was found in the cases of this series which came to autopsy. In one case with general dilatation of the aortic arch there was an aneurysm of the left axillary artery. Thoma figures an instance in which a secondary aneurysm arose through a rupture of the wall of the dilated aorta.

Symptoms. Dilatation of the aorta rarely exists alone, and hence it is difficult to decide which symptoms are due to it and which to associated conditions. When present alone, especially in old people, it may not cause any symptoms, as is proved by the discoveries of the autopsy room. Symptoms due to valvular disease, especially aortic insufficiency, myocarditis, coronary artery disease, and angina pectoris, may be present. The effort to eliminate these as far as possible is made in this study, and it is important to try to decide to what extent we have a definite clinical picture due to dilatation. I believe that in many instances the picture is characteristic, and

[1] Modern Medicine, iv, 463.

that the diagnosis can be made with reasonable certainty even before it is confirmed by a fluoroscopic examination. The history of a typical case brings out the general features.

The patient was a male, aged fifty-six years, a merchant by occupation. He came complaining of occasional uneasy feelings in the thorax, which he described as being rather more than oppression and yet less than severe pain. He was rather apologetic about consulting a physician, as he feared he might be thought to be making too much of a little thing. The family history was negative. In his previous history it was found that the patient had had diphtheria, measles, and typhoid fever. He had not been a specially heavy eater, but had always used alcohol rather freely. For some years he had been working at high pressure, carrying a great deal of responsibility and a heavy load of worry. There was no history of lues.

For about two years he had noted at times, especially with any sudden exertion, such as running for a car, or any unusual excitement, that he had a curious feeling in the chest. This was generally described as being in the sternum or a little to the left of it, although at times it was apparently more marked at the lower end of the sternum, and occasionally it radiated into both shoulders. None of these attacks were at all alarming, and he was always able to go on, although sometimes he had to rest a few minutes before doing so. No one had ever commented on anything strange in his appearance when they occurred. He himself thought it was needless to seek advice, but the continuance of the symptoms rather worried him.

The patient was the picture of robust health; he was well nourished and had a good color. The lungs were clear throughout. The visible cardiac impulse was not marked; the maximum impulse was in the fifth interspace inside the nipple line; the area of dulness was not increased, and except for a soft systolic murmur in the pulmonic area, the sounds were clear. The pulse was 72, of good volume and regular; the blood pressure was 135 mm. On inspection, there was a distinct lift of the manubrium and a visible pulsation in the first and second right and left interspaces. On percussion, there was dulness over the manubrium and to either side. On auscultation, both sounds were heard at the base, the second with a marked ringing, amphoric quality, which could be made out over

a rather wide area. The fluoroscopic examination showed a diffuse enlargement of the whole aortic arch, and a shadow could be seen both to the right and left of the sternum, continuous with that of the heart. This patient has been under observation for nearly four years and no material change has occurred, except that the "attacks" have decreased and are now infrequent.

Clinically there are several groups of cases, which usually can be separated without much difficulty:

1. *Latent Cases.* Absence of all symptoms is especially likely to occur in old people, and the condition is often found unexpectedly post-mortem. In this series there were nine patients in whom the condition was recognized only by the routine examination, as they made no complaint of any symptoms which suggested disease of the cardiovascular system. One was admitted for diabetes, one for chronic alcoholism, one for organic disease of the spinal cord, one for lipoma, one for diarrhœa, and the others for indefinite complaints. In all the diagnosis was confirmed by the fluoroscopic examination.

2. A group in which *cardiac symptoms,* suggesting failure of the heart muscle, predominate. In the cases with marked signs of valvular lesions, aortic insufficiency predominates. The picture is often that of cardiac failure, which is the final stage in the majority of cases, not because of the dilated aorta, but on account of the associated condtions.

3. A group with features much like those of *angina pectoris;* in fact, sometimes it may be difficult to say that angina is not present. There were fifteen patients in this series in whom the pain might be described as anginoid, and others gave a history of it. In all of those who had the attacks of thoracic pain while under observation it was noted that the severity was less than that usually seen in angina pectoris.

4. A group in which the symptoms are those of the condition in the aorta itself, the heart being practically normal. These patients often give a history of symptoms which suggests cardiac disease.

Complaint. This usually suggests some circulatory disturbance. The most frequent is shortness of breath and dyspnœa, usually not constant unless there is a marked cardiac condition present. Next in frequency is the complaint of thoracic pain of varying degree.

Œdema of the feet and legs, which in several occurred without the heart showing any signs of disease, is fairly common. Weakness is rather a frequent complaint, and loss of weight, cough, palpitation of the heart, syncopal attacks, giddy feelings, hoarseness, thumping in the chest and neck, change in the voice, and indefinite pains were also mentioned by some patients. Only one patient complained of difficulty in swallowing; this was verified by observation and occurred quite frequently. That certain patients had no symptoms referred to the vascular system has to be remembered in regard to the figures.

Onset. This was gradual in 41 and sudden in 10 (9 had no symptoms); in 3 of the latter it followed unusual exertion, in 1 injury, in 1 severe mental strain and exposure, in 1 the change to a high altitude, and in the others there was no definite cause.

Dyspnœa was the most common symptom, and occurred in 42 cases. Its severity depended largely on the state of the heart, and when this was normal it was usually brought on by special exertion or excitement. Cough accompanied it in 16 cases, in 3 with spitting of blood. A striking point in several cases was that the dyspnœa was quite out of proportion to anything that could be found to account for it.

Œdema of the feet and legs occurred in 16 cases. In several of these the heart seemed normal in every way, and, as a rule, the blood pressure was low.

Pain was a prominent feature in 20 cases. In 6 of these it was referred to the chest generally without any special localization; in 4 it was referred to the left chest; in 9 it was referred to the heart, and in 5 of these it radiated to the shoulder and arm (3 to the right, 1 to the left, and 1 to both arms); and in 1 it was on the right side of the sternum. The attacks of pain were usually not very severe, but sometimes continued off and on for some hours, and generally were not accompanied by any change in the patient's appearance. In only one case was there any note of sweating with the attack of pain. Walking against a strong wind, sudden exertion, excitement, and overloading of the stomach were all given as causal factors, by which angina pectoris is suggested.

Physical Signs. With the frequent association of various cardiac conditions it is natural to have signs due to them, but these require

no discussion and only features of dilatation are considered. A striking condition is marked fulness of the veins, especially those of the neck, upper thorax, and arms, the first named usually being the most dilated. The visible arterial pulsation is sometimes very diffuse, and often very marked over the carotids and subclavians. In several cases it was much more marked over the right than over the left carotid. The subclavians seem to be lifted higher than normal by the dilatation of the aorta and may be seen above the clavicles. There may be a visible swelling, as in two patients in whom a pulsating mass the size of a hen's egg was visible at the inner end of the right clavicle and in the episternal notch. With the enlargement of the aorta it would be expected that pulsation in the episternal notch would be frequently seen, and such is the case, as in 22 cases it was well marked.

A most important point on inspection is pulsation in the first and second interspaces. This is usually best seen with the patient lying down and the examiner with his eyes about on a level with the thorax; good light is essential, and the inspection should be from various positions in regard to the patient. An impulse may be seen in one interspace only or in any combination of the first and second right and left interspaces. The second right is the most frequent situation, then the second left, first right, and first left interspace. This visible pulsation, as a rule, is more diffuse and not so localized as in saccular aneurysm. In some cases it is more evident when the patient is sitting than when lying. It can rarely be felt distinctly, and does not give the feeling of being more forcible than the cardiac impulse; in fact, the pulsation in dilatation is usually more evident on inspection than on palpation. It does not lift the palpating finger, as may occur in aneurysm. There was a definite lift to the manubrium in 26 cases; this was usually better seen than felt. In 5 the absence of any visible heaving was noted, and in the remainder the point was not noted. In two cases the manubrium was prominent and there was a distinct lift of it and the inner end of both clavicles; in one, of the manubrium and right clavicle. In one the inner end of the right clavicle was lifted. In some cases it was noted that there was a widespread visible heaving, but no well-marked local impulse.

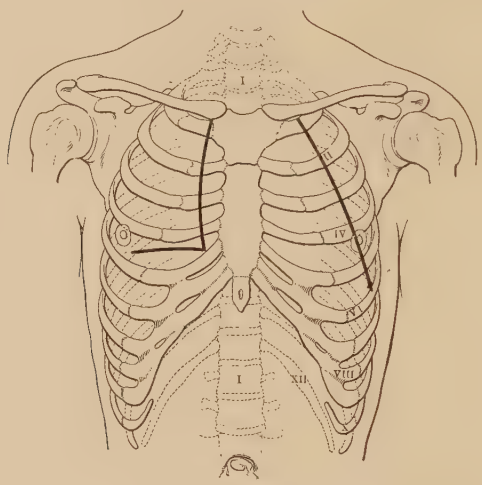
Pulsation in the back in the left interscapular space was observed

in one case only. In this case it disappeared after a period of rest, which usually results in a diminution in the extent of the visible pulsation in front.

Palpation. In a number of cases the aorta can be palpated in the episternal notch and the subclavian arteries above the clavicles. In one case there was a distinct pulsating tumor projecting above the inner half of the right clavicle and in the episternal notch; the finger could be passed between it and the clavicle. The heaving of the manubrium could be felt in 6 cases. The contrast between the marked *visible* lift of the manubrium and the slight *palpable* lift is often very marked. The shock of the second sound was felt at the base in 9 cases. A diastolic thrill was felt over the manubrium in 4 cases, and only in the aortic area in 4. In 1 case there was a marked diastolic thrill over the right sternoclavicular joint, the manubrium, and the upper half of the sternum.

Percussion. The results of percussion are perhaps the most important in the recognition of dilatation, and the finding of dulness over the manubrium in a routine examination may suggest the diagnosis. In 55 cases of the 60 there was distinct dulness over the manubrium. In 2 cases its absence was noted, 1 being with marked emphysema, and in 3 cases there is no note. The area of dulness was usually continuous with the cardiac dulness, and generally extended some distance outside the edge of the sternum, as a rule, both in the first and second interspaces. In 28 cases it was marked in the first and second right and left, in 7 in the first right and left, in 2 in the first left, and in 2 each in the first and second right and first and second left interspaces. The width of the area of dulness varies somewhat, the usual transverse measurement being about 7 or 8 cm. The widest was 14 cm. in the first interspace, and there were several with an area of dulness measuring 10 cm. across. As a rule, the dulness is more marked to the left of the sternum than to the right. The usual area of dulness is shown in the accompanying diagram. Changes to some extent of the area of dulness occurred in several cases, some increasing and some decreasing. In some patients who have been followed for years a definite increase in the extent of dulness has been noted. In one patient, who was bled 500 c.c. with marked benefit to symptoms due to cardiac failure, no decrease

in the area of aortic dulness was made out. The occurrence of an area of dulness, as described by Potain, extending from the manubrium in a segment of a circle to the right, with a shape like the "crest of a fireman's helmet," has not been made out.



The area of dulness in dilatation of the arch of the aorta.

Auscultation. When the second sound is present it often has a distinct quality at the base which is the most characteristic sign on auscultation, and in several instances first suggested the diagnosis. This is a bell-like, ringing, amphoric quality, very distinctive when once heard, and quite different from the accentuation found with high blood pressure. It has been given various descriptions, "clangoreux" by de Mussy, "bruit de tabourka" by Potain, "timbre métallique," etc. This sound may be heard over a wide area and with especial distinctness over the manubrium and in the neck over the carotids. It was well-marked in 12 of 22 cases in which the second sound was clear. In 5 cases with aortic insufficiency the second sound had this quality, and the diastolic murmur had somewhat the same. In 2 cases of aortic insufficiency in which the second sound had entirely disappeared, the diastolic murmur had this amphoric, musical quality. When aortic insufficiency is present the diastolic murmur may be heard with great distinctness over the manubrium and at the episternal notch.

Pulse. In the cases with no decided cardiac change there was no striking peculiarity. The rate was not particularly rapid; in about one-third of the cases it did not rise above 80, and in the same number was not above 100 as a rule. In 4 cases the rate was persistently below 70, in 1 being usually about 50 per minute.

Blood Pressure. It might be expected that this would be high and such a statement is made in the literature, but the results of this series show the contrary. Of course, in a condition which is so likely to be associated with other vascular lesions, there are many factors which influence the blood pressure. However, in the cases in which the aortic dilatation was the prominent factor the blood pressure was low. This may seem surprising when we consider the common sclerotic changes, but the alteration in the aorta must have considerable effect. The large vessels by their elasticity tend to convert the intermittent force of the heart into a continuous pressure. But when the aorta is dilated and has lost its elasticity, the blood is forced into a more or less rigid reservoir and a low pressure is the result. Among 48 cases with records, in 35 the average systolic pressure was below 140 mm. (Riva-Rocci instrument, broad arm-piece). In 3 of these it rose temporarily to higher figures. In 3 patients it varied from 70 to 95, never being above the latter figure, and with an average of 80. One of these had acute endocarditis on an old chronic process, with which he died. The other had quite marked arteriosclerosis with aortic insufficiency, and was discharged from the hospital in fairly good condition. Of the remaining cases, 9 varied from 125 to 180, and the others from 150 to 260. In the majority of these the higher figures were only for short periods, the pressure falling rapidly, in one case from 200 to 130, where it remained. Practically all the patients with the higher figures had cardiac hypertrophy; in the patients without marked changes in the heart the pressure was usually between 120 and 135. Crises of hypertension described by some writers were not observed in this series. Several patients with chronic nephritis (urine of low specific gravity, containing a very slight amount of albumin and a few casts), had a low blood pressure.

In 9 cases in which there were records of both the systolic and diastolic pressure, these showed a fairly steady difference of about

30 mm. Hg. This was practically the same whether the pressure was high or low.

Fluoroscopic Examination. This is a most important part of the examination, and in doubtful cases is usually the deciding point. Dr. Baetjer, who has had a large experience in thoracic fluroscopic examinations, gives the following description: "Dilatation of the aorta is marked by an increased width of the aorta. In normal conditions fluoroscopic examination reveals only the bend of the aorta projecting to the left of the sternum and just beneath the clavicle, the ascending and descending portions being invisible behind the sternum. In dilatation there is a shadow projecting to the left of the sternum and extending downward to be lost in the shadow of the heart. This shadow may vary in size and in extreme dilatation may project to the right of the sternum. This shadow persists between pulsations, showing that there is a true dilatation of the aorta. In neurotic individuals and when the blood pressure is low we frequently find the aorta, in pulsation, extending beyond the sternum, but between pulsations it invariably recedes behind the sternum and is lost to view." The degree of visible pulsation varies, but in the majority there is no great difference in the extent of the shadow during systole and diastole. In one patient with quite marked dilatation it was noted by Dr. Baetjer that the shadow to the left of the sternum did not vary, but that to the right did. This may have been due to the greater direct force of the flow from the ventricle on the first portion of the arch. In several instances it was noted that the shadow of the aorta extended unusually high in the thorax. Dr. Baetjer tells me that in several patients the position of the heart in the thorax seemed more horizontal than normal.

Pressure Effects. These are interesting in view of their frequency and importance in the symptomatology of saccular aneurysm of the aorta. In diffuse dilatation they are less frequent and less serious.

(*a*) *Vascular System.* Fulness of the veins of the neck, upper thorax, or arms occurred in about one-third of the cases. In 6 cases the radial pulses were unequal, in 4 the left being the larger and in 2 the right. The blood pressure was unequal in the brachials

in 3 cases, in 2 that in the left brachial being the higher. The difference varied from 13 to 18 mm. Hg. In one case the vessel with the larger volume had the lower blood pressure. The difference in the radial pulses may be due to some obstruction at the beginning of the innominate or subclavian artery, or the innominate or subclavian artery may be involved in the dilatation.

(*b*) *Respiratory Tract.* A tracheal tug was noted in 12 instances, in 4 of which it was quite marked for some time after admission, but with improvement in the general condition it disappeared. In one patient the tracheal tug was present on several occasions on admission, but disappeared under rest, and coincident with this it was noted that the area of aortic dulness had decreased. In some patients there was dulness at one or both bases, but this may have been due to the state of the heart. In 3 patients there was recurring hydrothorax on the right side, for which repeated tapping had to be done.

(*c*) *Nervous System.* There was inequality of the pupils in 9 patients. In 3 the left was the smaller, in 5 the right, and in 1 there was no note. The usual opinion has been that this was due to pressure on the sympathetic, but alterations in the circulation may be more important. There was pressure paralysis of the left vocal cord in 3 patients, and in 5 others the voice was hoarse and the cough had the "goose" quality. One patient has been under observation since 1905, at which time he had complete recurrent laryngeal paralysis of the left vocal cord, which has continued to the present. The first symptoms were two years before his first admission, when he had pain in the upper thorax, with suffocating feelings and a marked change in the voice.

In some cases the pain or numbness felt in the shoulders and arms was persistent. One patient had constant pain in the left shoulder, which occasionally radiated down the arm and to the scapula. In one patient pressure over the fifth, sixth, and seventh dorsal spines caused severe pain. The same patient had pain in the heart and left shoulder on firm pressure over the precordium.

(*d*) *Bones and Muscles.* There was no instance of perforation of the thoracic wall or erosion of the vertebræ.

(*e*) *Alimentary Tract.* Dysphagia was present in one patient. No attempt was made to prove the presence of obstruction.

It is rather surprising, perhaps, to find the pressure signs occurring as often as they do, although, of course, with less frequency than in aneurysm. They that should occur is not surprising in view of the anatomical conditions. In a previous paper on this subject[1] the view was taken that the pressure effects were comparatively few, but the study of subsequent cases has rather modified this view. Still the pressure effects are rarely serious.

Associated Conditions. Thickening of the palpable arteries was found in the great majority of the patients, and in 39 cases it was noted as being marked. In 5 there was calcification of the vessels. Aortic insufficiency was present in 27 cases, in 18 with mitral insufficiency, in 3 with aortic stenosis and mitral insufficiency. Mitral insufficiency without an aortic lesion was found in 4 cases, all having marked arteriosclerosis. The heart was practically normal, so far as could be made out, in 18 cases; in 5 others there was marked hypertrophy, and in 4 others slight hypertrophy without any valvular lesion.

Relative Aortic Insufficiency. This is rare under any circumstances, but dilatation of the arch of the aorta should favor its production. There were 2 cases in this series in which the signs suggested this condition.

The first patient was a colored female, aged thirty-two years, admitted March 25, 1898, with dyspnœa and œdema. She had marked fulness of the veins of the neck and upper thorax. The heart was enlarged to the left and there was a heaving impulse over the manubrium, with dulness, which extended into the first interspace on both sides. There was a well-marked systolic murmur at the apex and a definite diastolic murmur in the aortic area. The second sound could be well heard over the manubrium and in the neck. Later there was a diastolic shock at the base. The pulse varied from 70 to 80; it was not specially collapsing, and the pulse tracing did not suggest aortic insufficiency. The presence of the aortic diastolic murmur was noted by Dr. Osler. The fluoroscope showed dilatation of the arch. She was admitted six months later with marked dyspnœa and œdema. There was marked pulsation

[1] Canada Lancet, 1907–08, xli, 821.

in the episternal notch, but the heaving of the manubrium was not as marked as on the previous admission. Over the body of the heart the second sound was much accentuated, but no diastolic murmur could be heard. She died the day after admission. The autopsy showed arteriosclerosis, hypertrophy of the heart, pulmonary thrombosis, and dilatation of the arch of the aorta, with uncompensated degeneration in the intima and media. The aortic and mitral valves were normal. The aorta was much dilated and thin, measuring 9 cm. in diameter above the valves. It showed many areas of nodular thickening, and three areas about 1.5 cm. in diameter, which were very thin.

The second case was a man, aged sixty-four, who was admitted with dyspnœa and swelling of the feet. The heart was much enlarged, with a soft systolic murmur at the apex and a definite diastolic murmur in the aortic area. The second aortic sound had a ringing amphoric quality. Within a week the diastolic murmur had disappeared, to reappear later. Four months later he was admitted again with a curious continuous murmur best heard at the aortic area. At times it had a systolic intensification, but was very variable and markedly altered by changes in the patient's position. The diastolic murmur was not heard on later examinations.

The infrequency of relative aortic insufficiency is well recognized, and the experience of this series does not support the view expressed by Balfour,[1] that "when once dilatation of the ascending aorta is produced, the secondary development of incompetence of the aortic valves is only a question of time." Some of these patients have been under observation for years and an aortic murmur has never been heard.

Renal System. This showed changes in the majority of cases. A number had chronic nephritis; others had albumin and casts or albumin alone.

Blood. This showed no changes of any moment. The count was about normal in the majority, a few showing secondary anemia.

Intestinal Hemorrhage. One patient, a colored man, aged thirty-three years, had several large hemorrhages from the bowel, for which

[1] Clinical Lectures on the Diseases of the Heart and Aorta, London, 1882.

no cause was found. This is interesting in connection with the observation made by Albers, of Bremen, and quoted by Dr. Osler,[1] in which hemorrhage of the bowels occurred with dynamic dilatation of the aorta.

Course. In so far as dilatation of the aorta is concerned, apart from other cardiovascular lesions, there seems no reason why it should not continue indefinitely. It is the associated conditions which are of moment in the prognosis. One patient in whom the condition was recognized in a routine examination has gone for five years without any evident change, and without any symptoms which might be referred to the condition of the aorta. Serious accidents, such as occur in saccular aneurysm, were not noted in this series. There was no instance of rupture of the aorta, although it seems possible that this might occur, or of dangerous pressure signs. The mode of life must have considerable effect on the outlook, and patients who can live a quiet regular life may go on indefinitely. Unfortunately in many of the patients the occupation is an important factor in the etiology, and they are often unable to obtain easier work. Occupations involving sudden severe exertion have a very detrimental effect. In the majority of cases it is probable that the condition of the first inch of the aorta will largely determine the outlook. With serious disease of the aortic orifice or interference with the coronary circulation, the prognosis is grave.

Diagnosis. It is important to recognize the frequency of the condition and to be on the watch for it. The complaints usually suggest disease of some other organ, and the physical signs may not attract attention—they have to be looked for. There are two groups of cases in which the diagnosis may be suggested. In one the history and symptoms suggest cardiac disease, but on examination no disease of the heart is found. In the other group the history of thoracic pain may suggest angina pectoris, but careful scrutiny does not bear out this diagnosis. In many cases the dilatation of the aorta is accompanied by cardiac disease, and it is easy to rest satisfied with the recognition of the most obvious process. Of the physical signs, the visible impulse seen over the manubrium and in

[1] A System of Medicine, Allbutt and Rolleston, 1909, vi, 669.

the adjoining first and second right interspaces, the area of dulness, the curious amphoric quality of the second sound, if this be present, and the fluoroscopic examination give the greatest aid.

Various other intrathoracic conditions have to be considered, the tendency being rather to regard dilatation as being one of these than the contrary.

1. *Saccular Aneurysm of the Aorta.* The view may be taken that there is no need to attempt to distinguish between saccular aneurysm and diffuse dilatation of the aorta. This, however, is not correct, because the treatment is entirely different. To attempt to wire a diffuse dilatation of the aorta could not possibly be of any advantage and would do harm; while as regards a prolonged period of rest, it is doubtful if this is indicated in diffuse dilatation. The outlook is also quite different, being much less favorable in saccular aneurysm. The points in the differential diagnosis are as follows:

(*a*) *Pulsation.* As a rule, the visible pulsation is more diffuse and widespread in dilatation, and an important point is the difference on palpation. The impulse in the interspaces in dilatation may be readily visible, but cannot be felt, while in the sacculated aneurysm it is more punctate and readily palpable. Very often the pulsation of a saccular aneurysm is more forcible than that of the heart. The heaving impulse of the manubrium is not readily felt in diffuse dilatation and the impulse in the interspaces may not be palpable.

(*b*) *Percussion.* The area of dulness in dilatation is more or less regular. It is found over the manubrium and perhaps on both sides of it, usually rather more to the left. As a rule, it is continuous with the cardiac dulness, whereas in saccular aneurysm very often an area of resonance is found between the cardiac dulness and that of the aneurysm. In only one instance of this series was dulness made out in the interscapular region and this was only temporary, disappearing under rest.

(*c*) *Auscultation.* The curious quality of the second aortic sound, already referred to, is very significant when present. The wide area over which the second sound and the murmur of aortic insufficiency, if present, is heard, may be an important point.

(*d*) *X-ray Examination.* This gives information of the greatest value, and in a doubtful case must be the deciding test. Naturally

its value depends on the experience of the observer. The possibility of atypical pictures due to some unusual position of the aorta must be kept in mind.

(*e*) *Pressure Effects.* These are decidedly less in dilatation than in aneurysm, but, as noted in the discussion of the physical signs, they may be marked. Severe pressure signs, especially thoracic pain, speak against dilatation and for aneurysm. Certainly, continuous pain is rare in dilatation and the evidences of severe pressure, dyspnœa, stridor, etc., are apparently unknown. The variation in the pressure signs in dilatation has been noted.

2. *Intrathoracic Tumor.* This may give difficulty, but the pressure signs of tumor are likely to be more marked. The visible pulsation, usually so characteristic of diffuse dilatation, is not likely to be present. In a case in which there is doubt from the physical signs the examination with the fluoroscope will usually settle the question at once.

3. *Malposition of the Aorta.* If the aorta is unusually twisted, and lies further to the right than usual, there may be visible pulsation to the right of the sternum and an increase of dulness, or in patients with scoliosis, the vessel may be out of the normal position. The same may be seen in some of the thoracic deformities due to rickets with displacement of the heart and aorta, or in instances of marked changes with shrinking of one side of the thorax. The general features should suggest the diagnosis, and if there is doubt the *x*-ray examination would decide without difficulty.

In the distinction between saccular aneurysm and dilatation or malposition of the aorta, the continuance of the signs and symptoms without any great change has to be kept in mind. While a saccular aneurysm may show but little change during a considerable period, as a rule it tends to be progressive. In the absence of cardiac features, diffuse dilatation may apparently go on indefinitely without any marked change.

4. *Angina Pectoris.* The complaint of thoracic pain may suggest this diagnosis, and until the patient can be observed for some time a decision may be difficult. There is no reason why pain similar to that of angina should not occur in dilatation, especially in view of the explanation which ascribes the pain of angina to disease of

the first part of the aorta. There are certain features which are generally distinctive. The pain in dilatation is rarely so severe as in angina, is often described as more a feeling of oppression than of pain, may persist for longer periods, occurs not infrequently on the right side, and is sometimes felt in both arms. This last should always suggest dilatation. The pain in dilatation does not often seem to be caused by exertion, in fact several patients found that moderate physical exertion relieved the pain. In only one case did sweating occur with the pain. In no case, so far as known, has death occurred during an attack of pain.

5. *Cardiac Disease.* As Hodgson emphasized, the symptoms of dilatation of the aorta are often regarded as due to cardiac disease. When this does not co-exist a careful examination should prevent any mistake.

TREATMENT. Any associated vascular condition, valvular or muscular insufficiency, or myocarditis, demands its usual treatment. When present, so far as treatment is concerned, they give the usual indications. As regards dilatation itself, the main points are as follows:

Rest. There is no universal rule, and the question must be decided for each patient. If there is pain, dyspnœa, distress, or œdema of the feet, a period of absolute rest is advisable until relief is obtained. But rest should not be too prolonged, and in an ordinary case there does not seem any advantage in more than two or three weeks. Prolonged periods of physical rest are not advisable, and rest from worry and the strain of daily troubles seems more important. A long vacation is advisable if it be possible. In the laboring classes, to which so many of these patients belong, the problem is more difficult. Occupations which involve severe strain should be given up and every effort made to have the patient employed at some lighter task. When the patients are free of symptoms a certain amount of exercise is an advantage, if the associated conditions do not forbid. Several of the patients in this series find golf an excellent form of exercise.

Diet. This should conform to the general rules for arteriosclerosis. Reduction in the amount is most important, and meat especially should be limited in amount. Alcohol is best omitted, and fluids should not be taken in large amounts.

Bowels. It is most important to keep these freely open, for constipation seems to be especially harmful. Such purgatives as senna, aloes, cascara, and phenolphthalein may be given, and an occasional mercurial (nothing is better than 5 grains of gray powder) may be given at night followed by a saline in the morning.

Medicinal. There is no drug which can have any marked effect on the aorta, for the damage is done. Potassium iodide should always be given and small doses (3 to 10 grains) are probably best, over considerable periods of time. The vasodilators are usually not indicated; if high pressure is present they may be tried cautiously. Digitalis is not indicated for the aortic condition alone and may do harm. For the attacks of pain—if severe enough to demand treatment —codeine may be given by the mouth; morphine is rarely required, but should be given if the pain is very severe. Some patients, even with a low blood pressure, find that nitroglycerin ($\frac{1}{100}$ to $\frac{1}{50}$ grain) gives almost immediate relief, and there can be no objection to its use. Others find relief from a dose of aromatic spirit of ammonia (ʒi) with spirit of chloroform (♏xv).

In general, it may be said that a quiet even life, with avoidance of physical and mental strain, a diet limited especially in amount, open bowels, and meeting special indications when necessary, are the main points. With these we may hope to give the patients in whom the heart is not markedly affected many years of comfortable life. When cardiac breakdown appears, it must receive proper treatment.

Conclusions. 1. Dilatation of the aorta, considered apart from aneurysm, is relatively common and probably occurs more frequently than aneurysm.

2. Two main etiological factors stand out—(*a*) acute infections, notably rheumatic fever, and (*b*) those which cause general sclerotic changes.

3. The symptoms often suggest disease of the heart itself.

4. The physical signs are often very definite, of which visible pulsation in the upper interspaces, dulness over the upper sternum and adjoining interspaces, and the fluoroscopic examination are the most important.

5. Pressure signs are comparatively common, but are rarely severe.

6. The diagnosis can usually be readily made from aneurysm.

7. The outlook as regards dilatation is good.

LATER NOTES ON PHYSICAL EXPLORATION AND TREATMENT OF HEART DISEASE, WITH A FINAL WORD ABOUT OPERATIONS AND HEART FAILURE.

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To anyone who is ignorant or thoughtless, some present-day methods of managing sufferers from cardiac disturbances would seem to be a great and desirable advance over previous well-tried practice. But is it so? I fail to be convinced, and shall give a few clinical observations of my later years to justify my affirmation.

It is not very long since the sphygmograph in some form, and more or less improved as years passed, was the accepted and time-honored means of examining the pulse in a scientific manner, so-called. Plain tactile sensations of the older, experienced physician were not deemed sufficient accurately to determine facts pertaining to rhythm, force, intermittence, irregularity of pulse beats. It was essential, as was stated, to have definite, well-registered tracings that the eye could see and the brain interpret and compare. Singular to say, despite much long-continued and various work on the part even of skilled observers, the sphygmograph has, to a large extent, disappeared from practice, private or hospital.[1] In its place we now have the sphygmomanometer, and in connection therewith we have already the careful, selected, and admirable work of many men in our profession whose enthusiasm and talent make us proud, and justly so, of those who follow the older ones.

[1] The newest and most practical hospital polygraph (including sphygmograph) with which I am familiar is that of Barringer. It is described and pictured in the November number, 1909, of the American Journal of Medical Sciences, page 727. After reading the description, even without seeing the instrument manipulated, one must conclude that to be really useful requires much skill and habit.

But shall this new and improved instrument, which speaks to us by the rise and fall of the column of mercury or alcohol, and seems to tell the intellectual as well as the physical eye the strength and force of heart beats through the rise and fall of blood pressure, endure for any great length of time? I scarcely think so, judging by the past and judging by what is revealed to me with the use of this instrument as with its predecessor—at one time equally vaunted and followed.

No mere mechanical contrivance can possibly register accurately vital force, or translate it to us in a thoroughly reliable and authoritative way. This force varies too much, too continuously, with every different person of whatever age, sex, or occupation. It varies also with every passing emotion, and almost every accidental condition of place or surroundings, and, of course, with the influence and effect thus occasioned.

It should be admitted equally that the instrument, to be at all trustworthy, must be manipulated by one who has experience and intelligence and almost daily habit in its use. Again, even the observations of such a one are relative in the main, and comparable only in a truly serviceable way when made in regard to the same individual and under essentially the same conditions of life and occupation.

Change of diet, change of work, mental or bodily, change of instrument and technique, such as we should have with change of expert observers, will modify or alter considerably the reported record, and especially in variable, inconstant cases, in which closest observations and best interpretation thereof are alone valuable.

In this connection Leonard Hill[1] writes that "blood pressure reading should be taken under uniform conditions, with patients lying horizontally, not emotionally excited, not after exercise, not after taking hot food, tea, coffee, or alcohol, and not after the hand or wrist has been warmed or chilled. The pressure should not be read when it is first raised, but after it has oscillated up and down several times, since this gives a more accurate index, especially in the leg arteries. The reappearance of the pulse gives the pressure more exactly than the disappearance."

[1] Amer. Jour. Med. Sci., November, 1909, p. 753.

The preceding quotation proves that even the sphygmomanometer, which is frequently claimed to be so simple and practical as to require relatively little time or care in its use, to obtain reliable data, must now be judged differently with more perfect knowledge.

All this, and much that might be added, are only again confirmation of the important fact, ofttimes repeated, and yet never old and timeworn really, that the art and science of medicine must ever remain widely apart in many particulars. If the body were a mere mass of organs, whose size, weight, appearance, structure, could settle definitely and invariably their functional power and activity, then mechanical apparatus and purely physical methods would be everything we could desire, but such is far from being the case, as we know.

And thus it is we are forcibly obliged to return to the things and to the knowledge of very ancient date and treat them with increased and well-merited respect. Consideration for old-time methods must still come to the fore, and the erudite touch combined with the translation which comes through inward appreciation and feeling—the final outcome of lifelong work and observation—is, after all, our most valuable asset.

To the foregoing should be added a few words about the *x*-rays as an aid to diagnosis in diseases of the heart. In many instances already it has proved very valuable, and each day, in accuracy and perfection, it is advancing notably. On the other hand, as shown by L. F. Barker,[1] certain errors are to be avoided in its use which only great skill and practice can surely overcome.

"By means of diagrams, Barker describes the various shadows which the heart may give under different conditions and from different directions."

Cardiagraphy is, therefore, to be prized much more by the advanced worker in hospital wards than by the practitioner in his daily routine of private work, and even in the wards "errors to be avoided in the use of the *x*-rays" are not easily mastered. While useful as an aid to a well-thought-out diagnosis, it (the *x*-ray picture) is dis-

[1] Bulletin of the Johns Hopkins Hospital, October, 1909; also Boston Medical and Surgical Journal, November 25, 1909, pp. 795 and 801.

tinctly subordinate to our regular procedures as they have been marked out for us by the master minds of our profession.[1]

Let us now for a moment consider percussion and the orthodiagraph. Hitherto percussion of the heart, as of other organs, has seemed to be our most accurate way of determining its size, configuration, situation. With the new instrument, shall we soon abandon percussion, or look upon it as second best? I do not think so, and for one or more of the reasons already given in speaking of the sphygmomanometer.

Further, in this connection I would cite Drs. Clayton and Merrill, who write: "Satisfactory use of this instrument, as is the case with many others, such as the microscope or stethoscope, necessitates practice and a thorough familiarity with the normal."

"The skiagram usually requires long experience to interpret correctly," . . . and, "as a rule, percussion may be depended upon for clinical purposes;" . . . yet "in some subjects it was absolutely impossible to outline the heart by percussion," . . . "and alterations in the shape of the organ (heart) are determined more accurately by means of the orthodiagraph."[2]

Personally, it is true I have had no experience with the practical use of the orthodiagraph. Thanks, however, to the great courtesy of Dr. I. Adler, of New York City, I was able to see the working of the instrument at his house on the evening of January 12, 1910.

In a letter to me, from Dr. Adler, November 9, 1909, he writes as follows: "I am using the orthodiascope (also called orthodiagraph) more than ever, and grow more enthusiastic about it every day. It is of immense value to me, not only in corroborating and confirming the results obtained by auscultation and percussion, and allowing of more or less exact measurement, where formerly we had only guesswork, but, above all, on account of its opening up entirely new points of view in diagnosis. . . . I will frankly say that I would not like to do clinical work without the orthodiascope."

To this I would add, having witnessed a practical demonstration of the instrument at Dr. Adler's house, with Dr. Adler, Dr. V. H. Norrie, Dr. Walter Mendelson, and Dr. Adler's able associate

[1] Minor, New York Med. Jour., March 19, 1910, p. 578.
[2] Amer. Jour. Med. Sci., October, 1909, pp. 549–562.

present, that while I cannot admire too much the knowledge and skill of Dr. Adler and his associate, I am of the opinion that the orthodiascope must be limited in its use, except in a relatively few instances, to hospitals, with able and trained assistants. Otherwise, I do not believe the orthodiascope will have, even later, *real* value in clinical medicine and in our efforts to cure disease. It should be seen and understood by all; it should be, or rather will be, utilized by a very select few.

The electrocardiogram is the most recent addition to our knowledge relating to physical exploration of diseases of the heart, but here even more than with the cardiogram (taken by means of the orthodiagraph) and sphygmogram, the instruments employed are costly, cumbersome, complicated, and require for their intelligent use specially skilled and expert assistants.[1]

When we come to the use of medicinal remedies, what do we find? Frequently the so-called scientific observations taken by physiologists, first of all, in their experiments upon healthy animals, which differ very much and in very many ways from man. After the physiologists are through with their investigations, it is then the hospital, the laboratory, or the deadhouse which gives us another working basis of observations and results.

Finally, however, it must be the careful and intelligent art of the wise, sympathetic, experienced physician who, outside of hospital wards, attends the patient day in and day out, not to speak of the night watches, and who finds out really what are his most reliable drugs, when and how to use them to best advantage, what their indications are, and what their drawbacks.

It is a favorite notion of the moment that with heightened blood pressure digitalis should not be used. Knowing its effect upon the peripheral arteries, this seems reasonable, and in many instances it is wisdom to be followed. But there are exceptions, and I have in memory many a case in which digitalis has been serviceable, and despite the contraindication of hypertension and increased blood pressure. It was simply because blood pressure was a permanent

[1] Diseases of the Heart, by James Mackenzie, 2d ed., p. 370; also, Le Télécardiogramme, by W. Einthoven, Arch. Internat. de Physiologie, 4, 1906–07, p. 132. Thanks to the courtesy of Dr. Walter B. James, of New York City, I have had the privilege of seeing his demonstration of the use of the instrument in its latest improved form.

factor, so to speak, and the first and primary indication for treatment was to increase cardiac power, which was done effectively with digitalis.

There are times, of course, when the untoward effect of digitalis on the peripheral arteries is only well neutralized by some vascular dilator taken with it—notably by nitroglycerin, or the nitrites.[1] Unfortunately, it is frequently difficult to know just when and how much nitroglycerin, or the nitrites, to give, as their action is relatively rapid and evanescent as compared with that of digitalis, which is eliminated slowly from the economy. But in instances where arterial changes are permanent and considerable, as is often true past middle life, or sooner in alcoholic or syphilitic patients, nitroglycerin or the nitrites, even in large doses, and continued for some time, have little or no appreciable effect, bad or good. In some cases also, as Hare[2] very wisely writes, "we must endeavor not to bring pressure to the normal, but recognize that while the arterial pressure is too high, and must be lowered, it is, nevertheless, essential to bear in mind that a tension higher than normal is essential if the blood is to be driven through rigid and narrow blood paths." I beg to add, that in reasonable doubt it is wiser and safer not to attempt to lower pressure, but regard it as evidence of a natural and conservative process, and especially is this true whenever the patient is free from unpleasant subjective symptoms.

After all is said, we are obliged to return to old-time knowledge. When digitalis causes much slowness or irregularity of pulse, when, in addition, there is nausea and pallor, and no favorable reaction noticed in any way, we shall act most wisely in stopping it altogether for a while, or in giving it in small doses and, it might be, at longer intervals.

The form of giving digitalis is not unimportant. To obtain its most powerful effect, the fresh infusion from good English leaves is usually the best; when nausea is marked, or the stomach intolerant, and we feel we must try it, no preparation equals the tablet triturate, the best homeopathic ones appearing to me the most reliable for

[1] According to Hare, atropine is the most useful drug to overcome vascular relaxation without directly stimulating the heart muscle to increased endeavor.—The Therapeutic Gazette, October 15, 1909, p. 689.

[2] The Therapeutic Gazette, October 15, 1909, p. 688.

cause. They are made from tinctures prepared with the fresh plant and most carefully compounded.

In a few cardiac cases crystallized digitalin is most effective; and occasionally, when every other combination of digitalin fails, Trousseau's diuretic wine is a very saving help in time of greatest need.[1]

Now, much of all the foregoing is the result of experience—empirical, and backed up with no recorded scientific notes or data. It is the outcome of watching and doing during a lifetime; it is invaluable to know, and should not be overthrown, in my judgment, by any researches of even the most careful and judicious among the scientific workers. It is true, and must be admitted—*precisely why*, there may be many theories, but which is the wholly true one time alone shall ultimately decide, and perhaps never.

For many years we have had constant reminders of the great power and efficacy of strychnine as a most valuable and rapid heart stimulant. Occasionally the statement is true, but in many instances incorrect. To some patients strychnine proves of very little, if any temporary va ue, and when taken continuously for a time, and even in moderate doses, wakefulness, irritability, increased nervousness, are undoubtedly produced, and without any appreciable gain in general strength or vigor.

Both caffeine citrate in tablet form and strophanthus in tincture are far superior in the majority of instances; but with the first of these we may get unpleasant effects in some persons and from moderate doses. I have known as little as 1 grain of caffeine cause undue stimulation of the nervous system, and only half the amount could be given at a dose without evident injury to the patient of a temporary but somewhat disquieting nature, since depression seemed to me to follow rapidly after undue exaltation.

A word also in regard to the other drug. It must be known that we are using the best strophanthus by mouth or hypodermically,

[1] While digalen is said by some to be a good substitute for digitalis, Müller reports that it (digalen) differs but little in its action from other preparations of digitalis, and has no marked advantages over them, Amer. Jour. Med. Sci., November, 1909, p. 766. Again, E. H. Squibb claims good effects at times from the combined use of digitalis and nux vomica in preference to giving digitalis alone. With both drugs he makes use of the tincture.—Personal letter. October 26, 1909.

if we may expect from and count upon it as a helpful cardiac stimulant or tonic. This important fact is frequently ignored in practice.

These observations might be readily added to, but I trust they will, even brief as they are, serve the purpose of bringing forth new thought and fresh discussion.

A word may be added usefully on the subject of exercise—of walking. While I approve of walking at the proper time, and in almost all forms of heart disease, I insist upon its strict regulation, according to the stage of the disease and the strength of the patient. Again, while I have remarked benefit to result from increasing the length and duration of the walk on the level, I am not sure of its evident utility at times in making ascents, even carefully graded ones. I doubt very much the value of Oertel's theory and practice in this regard, and I have learned rather to dread even short ascents when at all rapid, and I am also convinced that longer ones, where the gradation is more even and the ascent less pronounced for a short distance, are to be advised only with extreme care and prudence. The going upstairs, the rapid doing of some act which requires the output suddenly or rapidly of an undue amount of effort, gives a strain to the weak heart which it requires sometimes days, and even weeks, to recover from.

In older people, and especially after long illness, we cannot be too solicitous and careful in this regard. Heart strain is then very readily caused, and to undo its evil effects is difficult and occasionally very disheartening.

In this category I would particularly direct attention to instances of cardiac irritability, or cardiac neurasthenia, brought on by several factors, no doubt, but among them should be especially emphasized, so as to be neutralized or avoided later, the disastrous results of continuous overwork—bodily, or of undue continuous mental effort, or of both combined. Daily routine, with many cares and anxieties and few or no respites, finally breaks down the most vigorous health and the strongest will.

When this has unfortunately occurred, it requires much time, continuous care, appropriate doing, and proper medicinal means to reëstablish a healthful balance. For a long while undue exertion,

emotional excitement, or worry will cause directly inappetence, indigestion, and insomnia.

And the sum of all these will very soon make a very ill patient out of one who seemed to be on the fair road to recovery.

In these latter remarks I am having in view more particularly the nervous disorders of the heart without apparent organic changes. And yet, with middle life or advanced years, we cannot be always sure that myocardial changes in subtle organic forms are not present, and are not indeed the essential underlying factors of many disquieting and for a while otherwise unexplained symptoms of impaired strength and nutrition.

Occasionally in such instances, and when all the ordinary cardiac remedies and nerve tonics, with change of scene, change of air, and prolonged rest, had failed to effect a complete cure, the addition of iron and manganese in a soluble form to a quinine tonic has apparently accomplished the greatly desired result.

Olla podrida, if you will, and the rationale of it I deplore, yet the outcome of its taking was the end most hoped for, namely, health, and the basis of its utility some blood defect possibly, although anemia was not invariably noted by an accurate blood count and differentiation or an estimation of the amount of hemoglobin proportionately.

How often do we read in the daily papers of an operation performed successfully, as stated during the first day or two, perhaps, and yet later bulletins speak of the very precarious condition of the patient. It may be that this unfortunate aftermath is the result of something unforeseen and possibly irremedial. Or, it may be, while the condition of the patient was considered as carefully as possible prior to the operation, and it was determined judiciously that the patient was in good shape to have the operation performed, with good hopes of a rapid and complete recovery from it, yet, despite the probabilities, trouble and danger had suddenly become manifest. Apart from the foregoing instances which we all recognize, and although we deplore, we would not change for the while and until knowledge is greater and more accurate, there are other examples of a far different order. Not infrequently operations are undertaken which are not justified simply because there is no need of an

operation; or, if there be, in a sense, need of them, they are not permissible to the upright surgeon, because the result to the patient, even if successful, is more than questionable as regards ultimate benefit.

Admitted that the patient will almost surely recover from the operation, and that the operation itself entails practically very little or no risk to life, yet the ultimate outcome, so far as health or usefulness is concerned, would be doubtless *nil*. Why, then, undertake them? Certainly not to gratify personal vanity or ambition, or, worse still, to add to the amount of ill-gained lucre.

But there are examples, and we read of them almost daily, where no fault could be found with the skill of the surgeon in a technical way; with his probity and care and good intentions, primarily.

But, to say the least, his judgment is faulty and his mental horizon limited, because of lack of instruction in most important by-paths of his work.

And here comes to the front, above almost every other consideration, the role of the heart in the economy—the first of all the organs in the vast number of cases involving life and death. If the heart be weak functionally—if it be unable to bear the strain of a formidable operation and all the necessary calls made upon its power during and immediately subsequent to the operation—in what way can the patient be benefited by any operation?

A heart may be enlarged, have perhaps one or more pronounced organic murmurs, and yet be functionally able to withstand even a formidable operation.

On the other hand, given a patient who is evidently much below par—run down in body and mind, from overstrain in one way or another, and perhaps during many previous weeks or months—and the heart of such a one may give way suddenly and death occur, and despite every known means being used intelligently to ward it off at the time of the final "heart failure."

Here, indeed, prevention is highest wisdom, and not the so-called cure, and sometimes it means proper management of fever which is present and possibly due to existing toxemia.

I know of no more difficult, uncertain problem at times in medicine than the correct estimate of what a patient can stand in the way of

an operation, simply having the staying power of the heart in view. Here the personal equation is the one important thing, and which must be estimated with keenest judgment. And here, too, the wisdom and horse sense of the experienced, all-round practitioner triumphs immeasurably over merely advanced science of the schools backed up with the very latest means of physical exploration.

Moreover, "the failure of circulation may be due to functional causes as much as to a condition represented by appreciable structural change. The teaching of modern science has been too much in the direction that phenomena can be wholly explained by structure. This is not true of the working mechanism of the human organism, nor, indeed, is it true even of mechanical things."[1]

[1] Heart Disease and Blood Pressure, Bishop, 1909, 3d ed., pp. 78 and 79.

THE CORD LESIONS IN TWO CASES OF PERNICIOUS (ADDISONIAN) ANEMIA.[1]

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The following cases of cord lesion with anemia belong to that group first described by Lichtheim, in 1887, and by many observers since, especially by Putnam and Dana in this country, and termed by certain observers in Germany, pseudo-combined sclerosis.

The two cases whose records are presented were under the independent observation of several clinicians in three large hospitals of New York City. It is to these observers—Drs. W. Gilman Thompson, W. B. Pritchard, L. A. Conner, and T. W. Hastings—that we are indebted for the early records, extending back in one case three years, in the other five years. The first case we saw in Dr. Pritchard's service in the City Hospital, and the second case was under the personal observation of one of us for one year in the Cornell Dispensary and the City Hospital.

Case I.—*Under observation five years; symptoms and signs of pernicious anemia; no neurological features; at the postmortem the characteristic changes of pernicious anemia; in the cord, from the tenth dorsal to the first lumbar segments on the left side, there was swelling, with cavity formation, occupying almost exclusively the gray matter; patchy degeneration of the posterior columns, especially in the lower cervical region.*

The patient was admitted to Bellevue Hospital August 24, 1904, where he remained until December 13, 1904. The state of the blood during this time is shown in Fig. 1.

[1] Published in Amer. Jour. Med. Sci., October, 1910, also with somewhat fuller consideration under the discussion.

The following is a brief summary of notes made on admission: History of syphilis, with initial lesion nine years previously, and excess in alcohol. Two months before admission feet and legs swelled. Headache, dizziness on rising from recumbent position. Burning pain across abdomen. Numbness in hands and feet. Shortness of breath. Compelled on account of weakness to give up work. On examination, the diagnosis of pericarditis, chronic valvular disease and chronic catarrhal gastritis were made, in addition to that of pernicious anemia. The stools were negative for parasites and ova, and the gastric analysis showed total acidity of 0.00073, free organic acids and salts 0.00063, combined and free hydrochloric acid 0.

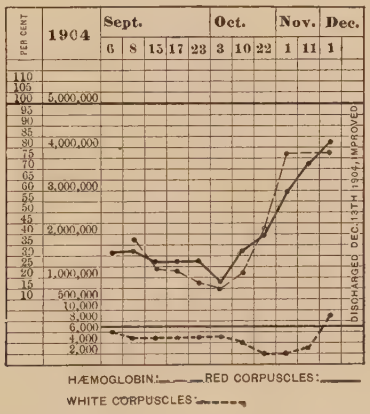

FIG. 1.—The blood chart of Case I in 1904. Microscopic examination showed the characteristic features of pernicious anemia. The highest lymphocyte count (October 3, 1904) was 37 per cent., with a polynuclear neutrophile count, on the same date, of 55.6 per cent. .Normoblasts were usually present; and reached 34 in a slide on October 10, 1904. At this time 9 megaloblasts were also found, but thereafter nucleated red cells were not seen.

There was nothing referable to the nervous system except persistent headache—pain over chest and abdomen—numbness on left side of body, extending to left side of face, tongue and lips. This latter condition occurred in paroxysms of about six minutes' duration. No objective disturbance of the nervous system was noted.

On December 13, 1904, he was discharged improved. Between this date and January 12, when he was finally admitted to the City Hospital, he was under observation at the Metropolitan Hospital,

Cornell Dispensary, and for a brief period (one week for alcoholism) at the City Hospital. The records from these clinics show that cardiac insufficiency, with valvular disease, alcoholism, with its accompanying gastro-intestinal disturbance, were the chief features. Weakness in the legs is the only note suggestive of any nervous affection. He labored in a drop forge and coal yard and at other occupations requiring considerable muscular effort.

When admitted to the City Hospital the condition of the blood was as shown in Fig. 2.

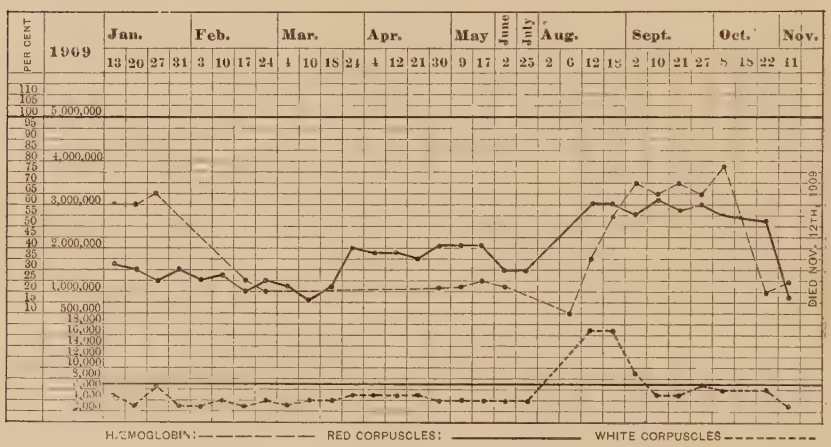

FIG. 2.—The blood chart in Case I in 1909. The microscopic examination was typical of pernicious anemia. The highest lymphocyte count was 45 per cent. (July 25, 1909); the polynuclear neutrophile count, at the same time, was 38 per cent. Nucleated red cells were a constant feature, megaloblasts preponderating.

The following is a summary of the clinical notes:

Male, aged thirty-eight years. Complains of pain in chest, dyspnœa, dizziness, faintness and tingling in feet and legs. History of sore tongue and bleeding gums of some months' duration. Examination shows well-nourished man, with good amount of adipose, yellowish skin. Heart shows signs of chronic valvular disease, with acute incompetency. Liver and spleen palpable. Other signs, were those of profound anemia. At no time was there any symptom or sign referable to the nervous system. Pupil reflexes were active, and knee-kick was present. No paresthesias were noted, and shortly before death the patient was walking about the ward. Up

to a month before his death the blood (Fig. 2) had been steadily rising, reaching nearly as high as it did five years before, when he had been able to return to heavy labor. A month prior to death, however, the blood count fell rapidly from 3,800,000 to 1,500,000. In view of the extensive changes in the cord found post mortem, all these clinical points are of considerable significance. Intestinal parasites, or ova, were not found. There was absence of free and combined hydrochloric acid.

The following notes are selected from those made between July 10, 1909, and November 12, 1909, the date of death.

July 4th, 1909.—Has been vomiting a great deal; takes little nourishment; restless at night; dyspnœa; moderate cyanosis; heart irregular; pallor much more marked; cheeks colorless; irrational at times; asthenia extreme; sways slightly when he walks, and requires assistance, but presents no peculiarity of gait. Confined to bed.

10th.—Condition gradually improving; nausea and vomiting stopped; appetite returned; cyanosis disappeared; dyspnœa slight.

August 8th.—Improvement more marked (Fig. 2).

30th.—Improvement steady; able to walk about unassisted; marked improvement in blood (Fig. 2).

September 22d.—Six or seven fluid stools daily for two days. Temperature, 102°; nothing in the physical examination to account for the temperature. No blood or mucus in the stools.

29th.—Stools and temperature normal. General condition good.

October 31st.—Up and about ward since note of September 29, but today he says he has not been feeling well for ten days; weakness; dizziness; roaring in head; precordial pains; loss of appetite; skin has undergone striking change in color (yellower). Returns to bed.

November 6th.—Is very dizzy even in bed.

11th.—Asthenia very marked. Lemon tint of skin very pronounced. Patient is drowsy, and he gives an expiratory grunt. Answers questions rationally. There is a jugular impulse synchronous with the carotid. Cardiac impulse distinctly visible and seen over a large area, but feeble to the touch. A systolic murmur to the right of the sternum different in character from that heard at the apex. Liver does not pulsate, but is readily palpable. Exami-

nation of feces negative. Urine examination showed occasional hyaline casts; faint traces of albumin; specific gravity between 1012 and 1030.

Examination of gastric contents, made on September 8, 1909, showed no free or combined hydrochloric acid.

11*th.*—Patient died.

Postmortem:[1] A well-developed male, rather poorly nourished, and apparently about forty years of age. The skin presented a uniform lemon yellow color. The sclerotics and external mucous membranes were not pigmented. There was a considerable degree of gingivitis, and the tongue was also very furred, but neither condition appeared more marked than that commonly found at autopsy in cases which have had other causes of death. The teeth were in fairly good condition. There were no scars, skin eruptions, or hemorrhages, superficially, anywhere, nor were the surface lymphatic glands or the thyroid enlarged.

The autopsy, done ten hours after death, disclosed the left pleural cavity containing 4 ounces of clear fluid, and the right 10 ounces of a similar fluid. The subcutaneous fat was rather less than normal in amount, and the muscles were of a bright, dark brownish red color. The peritoneal cavity contained no excess of fluid, and there was no chronic peritonitis. The pericardium contained 4 ounces of clear, straw colored fluid, and showed no evidence of pericarditis.

The heart weighed 400 grams, was soft and flabby, and all its chambers were slightly dilated. The tricuspid orifices admitted four fingers and the mitral three. There was no deformity or acute endocarditis of the valves. The right side was relatively more dilated, and the myocardium of the right ventricle was slightly hypertrophied. In the myocardium of the left ventricle, just under the endocardium, and particularly near the mitral orifice, was a typical thrush-breast appearance from fatty degeneration.

The lungs were slightly pigmented and œdematous. They were also uniformly somewhat emphysematous.

The bronchial and mediastinal lymph glands were not enlarged. The mesenteric and peritoneal lymph glands were all slightly

[1] Performed at the Russell Sage Institute of Pathology.

enlarged and of a pinkish white color. Microscopically, they showed a considerable proliferation of the lymphoid cells, many having become somewhat swollen and often containing some brown pigment.

The intestines were somewhat collapsed throughout and were rather transparent, and their lining mucosa appeared very smooth and atrophied. Microscopically, the glands were considerably degenerated, and in many parts disintegrated to a considerable extent from postmortem changes. In parts also there were some small aggregations of inflammatory large mononuclear cells.

The stomach was slightly dilated, its walls thin, and its lining mucosa smooth and atrophic. Microscopically, this mucosa showed some considerable atrophy and degeneration of the glands, but no marked inflammatory processes.

The liver weighed 1450 grams, was very soft in consistence and of a brownish yellow color. It gave a very marked, Prussian blue, reaction for iron. Microscopically, it showed an extensive fatty degeneration, particularly located in the inner half of the lobules, around the central veins. In these areas the liver cells were very extensively necrotic, while those at the periphery were much better preserved. No vascular thrombosis could be observed. There was also a very marked deposit of pigment granules in the liver cells, especially toward the periphery of the lobules. The greater part of this pigment gave the reaction of hemosiderin, and with prolonged staining practically all the pigment gave the Prussian blue reaction. The lining endothelium of the intralobular capillaries in occasional places showed a very marked swelling up, proliferation and specialization, the formation of blood constituents being in these places particularly easy to observe. There were also in considerable numbers coarsely granular eosinophile cells, with all sizes and types of nuclei, but mostly small, and with one or several nuclei, like those in a normoblast. These were attached to the wall of the capillary, as a rule, but also occasionally lay free.

The bile passages were clear. The gall-bladder contained a small amount of dark, inspissated bile, but no stones.

The spleen weighed 450 grams, was considerably enlarged, soft in consistence, and dark brownish-red in color, the Malpighian

bodies not appearing evident. It gave grossly a slight Prussian blue iron reaction. Microscopically, it showed a rather atrophic appearance of the Malpighan bodies. The sinuses all appeared somewhat distended, and for the most part contained a very large proportion of nucleated cells. Some of these cells resembled megaloblasts, and some, less frequently, were normoblastic in type. Many of these cells had the appearance of developing locally, rather of being collected from the general circulation. As in the liver, with considerable frequency, coarsely granular eosinophile cells could be seen, of all shapes, but mostly with one or several small normoblastic-like nuclei.

The suprarenal glands were both considerably atrophied.

The kidneys were slightly enlarged, and of a pale, brownish-yellow color. They gave a very distinct and rapid iron reaction, chiefly in the cortex. Microscopically, there was a very extensive fatty degeneration of the secreting tubules, and also a very considerable deposit of iron containing pigment.

The bladder and prostate showed no special change.

The pancreas also appeared well preserved.

The bone marrow in the centre of the shaft of the femur had a uniform dark raspberry color. Microscopically, the fat cells had almost all been replaced by a new cellular development. These new cells were mostly erythroblastic, there being megaloblasts and normoblasts in very large numbers. There was also a very considerable leukoblastic change, as there were very numerous collections of faintly acidophile myelocytes in all stages of transition. There were relatively only a very few eosinophile myelocytes.

The mastoids and tympani appeared healthy.

The cerebral meninges showed no abnormality, and the vessels at the base of the brain were well preserved. The brain was firm and in good condition. It was œdematous, but showed no other gross lesion. Microscopically, in the cortex, in several parts examined, and in the pons, no special lesion could be observed. The medulla, for the most part, showed no abnormalities, but several very small patches of degeneration in the posterior columns in the extreme lower part. The nuclei of the medulla appeared well preserved.

The spinal cord, however, presented somewhat extensive lesions. Although the autopsy was done ten hours after death, the brain and cord were removed from the body thirty-eight hours after this; 10 c.c. of 10 per cent. formalin were, however, injected in the usual site of lumbar puncture ten hours after death.

The membranes of the cord showed no abnormality, nor, grossly, did the entering vessels and nerves. There was no excess of fluid within the membranes, discounting the small amount of formalin injected. The cord, with the exception of one small portion, in its entire course showed no gross change, there being no shrinking, deformity, or softening, and was in a good state of preservation.

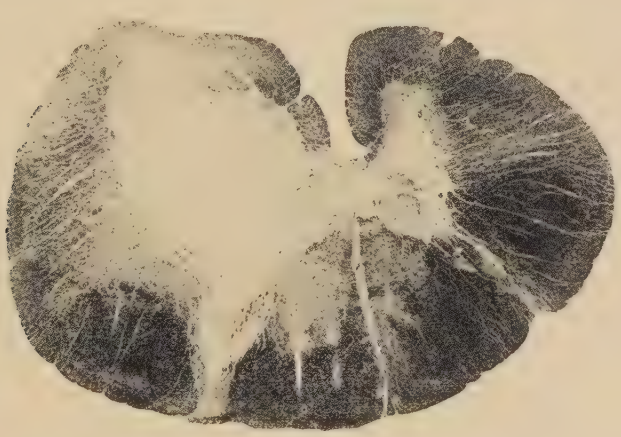

Fig. 3.—The spinal cord in Case I, showing extensive destruction of the gray matter of the left side.

This exception was between the level of the tenth dorsal and first lumbar segments, where, for a distance of about 2 cm., it was very much swollen on the left side. The right side opposite this did not appear to be affected. There was no communication externally from the interior of this swelling and no discoloration or meningeal change over it. The vessels, however, were somewhat congested on the surface of this part. On section of this swollen area there could be seen a very extensive destruction of the cord. A large space, containing a clear fluid, occupied a large part of the left side in this position. This space was not surrounded by any noticeable inflammatory reaction or sclerosis, yet it was rather well defined

It occupied almost exclusively the gray matter, and the process extended between the tenth dorsal and the first lumbar segments. In the upper and lower parts there was only a very small aperture in the gray matter, on the left side, and in the deeper part of the anterior horn. This cavity formation became gradually larger, until it occupied a very large part of the gray matter on the left side. In the middle portion, opposite the twelfth dorsal segment, the gray matter was completely destroyed, and the cavity extended out and laterally

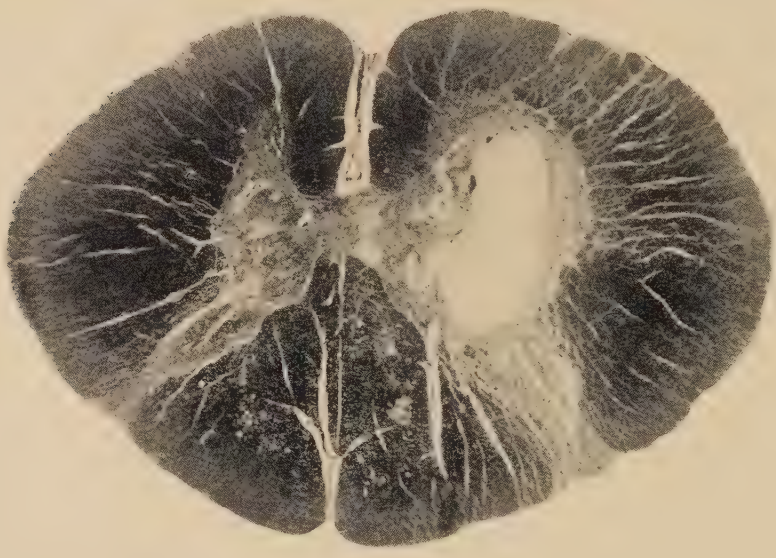

Fig. 4.—The spinal cord in Case I, showing destruction and cavity formation in the gray matter of the left side. (The specimen has been reversed.)

almost to the surface of the cord (Fig. 3). In all its length this process chiefly was located in the anterior horn, which, as the cavity became larger, destroyed it almost completely before the posterior horn was much affected, and even when the cavity was relatively very large, the posterior part of the posterior horn largely escaped damage (Fig. 4). In all situations this lesion caused, according to the size of the cavity, a swelling of the gray matter on the left side, particularly of the anterior horn.

Where the cavity, grossly, could not be seen, as in the upper and

lower extremities of this process, the gray matter on the left side, particularly anteriorly, appeared swollen (Fig. 5).

FIG. 5.—The spinal cord in Case I, showing swelling of the gray matter of the left side from œdematous separation of the tissues.

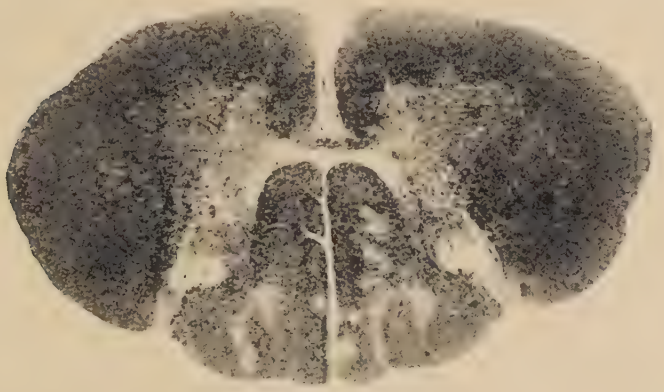

FIG. 6.—The spinal cord in Case I, showing patchy degeneration of the posterior columns.

Microscopically, there was a patchy degeneration in the posterior columns. In the lower cervical regions it affected irregularly a

large portion of both Goll's and Burdach's tracts (Fig. 6). In the dorsal region the degeneration was not nearly so extensive, but there were patches in the interior of the posterior columns in the entire course of the dorsal cord and upper lumbar segments, becoming less extensive from above downward. In the sacral and lower lumbar regions no degeneration existed. In these areas there was a disintegration of the nerve fibrils and also a considerable amount of replacement gliosis. There were numerous large vacuoles, sometimes containing remnants of degenerated nerve fibrils. In these same degenerate areas, however, always some healthy nerve fibrils remained, and some also showing a homogeneous swelling of the myelin sheath, very often associated with disappearance or disintegration of the axon. There were, however, no evidences of inflammatory reaction. The other columns of the cord showed no degenerative changes. The ganglion cells in the gray matter showed no particular change beyond, perhaps, a slight excess of pigment granules. In the area of extensive destruction, seen grossly, the tissues seemed more split up and distorted than necrotic. In those parts where the aperture, seen grossly, was small, the tissues were simply separated up, apparently by fluid. There was very slight or no inflammatory reaction around the cavity. There were occasionally a few leukocytes, but no hemorrhage around or in the disintegrated part. The cavity contained only some clumps of granular debris. In the greater part of this lesion, where the cavity formation was small, the nerve cells and tissues of the gray matter were simply separated up. Where the cavity was largest the nerve cells of the entire anterior horn were largely destroyed, but this was only for a short distance, and even in this place the cells of Clark's column and of the posterior root were comparatively unaffected. All the vessels in the affected area on the left side were surrounded by a wide space, as if from œdema, and several of the smaller capillaries and veins, especially just above where the cavity was largest, showed recent thrombi (Fig. 7). The pial vessels in the white matter and the vessels in the gray matter at the same levels on the right side, did not show any congestion and œdema. In this case, although postmortem processes may have to some extent influenced the appearances presented, yet it seemed to be the result of a thrombosis of some

of the small branches of the anterior spinal veins, with resulting effusion of fluid, with separation of the tissues, and some mechanical destruction of the related structures in the gray matter.

Fig. 7.—The spinal cord in Case I, showing the microscopic appearances of the gray matter in the section shown in Fig. 6. The small veins are surrounded by distended perivascular spaces and one of them is filled by a recent thrombus.

Case II.—*Under observation three years; symptoms and signs of pernicious anemia; headache; dizziness; tingling and numbness in the hands and feet for two and one-half years; six months before death there was spastic peraplegia and paresthesia; at the postmortem the characteristic changes of pernicious anemia; degeneration of the posterior and lateral columns of the spinal cord; extensive degeneration of the posterior columns and crossed pyramidal tracts, chiefly from the midcervical to the lower dorsal regions; slight degeneration of the direct pyramidal tracts.*

Case II presented the features of pseudo-combined sclerosis (Henneberg). The nervous manifestations were more or less present during the three years he was under observation, but when admitted to the New York Hospital the diagnosis of pernicious

anemia was recorded as the primary disease, and he was assigned to the Medical Division, while two and one-half years later, when admitted to the City Hospital, the case was regarded as primarily neurological, and he was assigned to that division of the hospital. The postmortem examination revealed the characteristic changes of pernicious anemia, and in consequence his early record was traced.

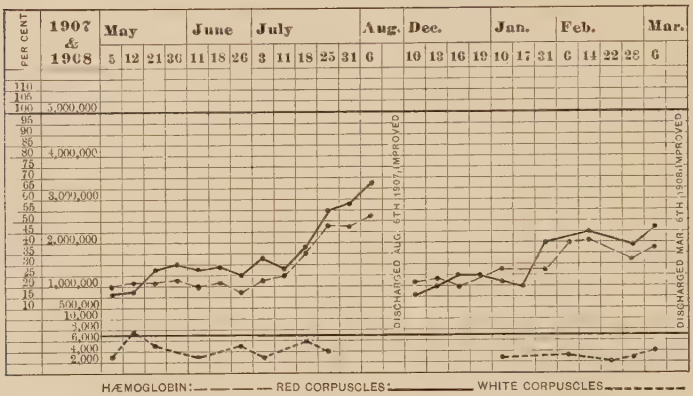

FIG. 8.—The blood chart of Case II. The microscopic examination was typical of pernicious anemia. The highest lymphocyte count was 58 per cent. (July 18); the polynuclear neutrophile count on the same date was 25 per cent. A striking feature was the absence, for the most part, of megaloblasts. Normoblasts were constantly observed, although not in great numbers.

He was admitted to the New York Hospital May, 1907. He denied having had syphilis, but gave history of alcohol in excess up to three or four months previously.

Fig. 8 shows the blood condition on his two sojourns in the hospitals, from May, 1907, to March, 1908.

There was slight fever, the temperature ranging between 100° and 101°. There were no marked disturbances of the nervous system found during this period. The following clinical notes are selected as indicating the condition of his nervous system at this time:

December 10, 1907. Knee-jerks not obtained.

January 7, 1908. Pain in chest; headdache; tingling and numbness in hands and feet.

February 11, 1908. Taking short walks on the street.

On leaving the hospital he was able to work (hotel clerk) for three months, but had to give up on account of weakness, and a few months later he developed cramps in both legs. He was not confined to bed, but sat at home, the weakness in the legs steadily increasing. This weakness continued to increase until August, 1909, when, on attempting to walk, he fell repeatedly. September, 1909, he was admitted to the City Hospital. The following is a summary of the notes upon his nervous condition.

On admission he was found unable to walk. Well developed male, aged fifty-five years. Skin is lemon color. Eyes negative. Upper extremities normal. The lower extremities give exaggerated reflexes, with spasticity. Skin hyperesthetic. Sensation to heat lost to below crest of ilium, with exception of inner surfaces of thighs. The blood shows oligocythemia and nucleated red cells and anisocytosis.

November 23, 1909. Patient is drowsy and incontinent of urine. Complains of abdominal pain. Mental condition good.

December 1, 1909. Knee reflexes absent. Tactile sense greatly diminished in lower limbs. Muscular atrophy marked, and there is great loss of power. Subcutaneous œdema and numerous vesicles have appeared over both legs. Bedsores over hips and sacrum.

5th. Patient died.

Postmortem.[1] A well nourished man, apparently about sixty years of age. There was no œdema and no scars, skin eruption, or hemorrhages. The skin was uniformly of a light lemon yellow tint. The superficial lymphatic glands and thyroid were not enlarged. There was a moderate degree of gingivitis, and the teeth were considerably decayed.

At autopsy, which was done fifty-one hours after death, the superficial fat was found to be in considerable amount, and the skeletal muscles were of a dark brownish red color. Both pleuræ were somewhat adherent posteriorly, but there was no fluid on either side. The abdomen showed no ascites or peritoneal adhesions.

The pericardium contained a few cubic centimeters of straw-colored fluid, but showed no evidences of pericarditis.

[1] Performed at the Russell Sage Institute of Pathology.

The heart weighed 425 grams, was very soft and flabby, and slightly dilated in all its chambers, particularly on the right side. There was in this case no thrush breast appearance from fatty degeneration in the left ventricle, but the myocardium of the whole heart was evidently very considerably degenerated. The aorta and larger vessels were very well preserved.

The lungs were œdematous and very emphysematous.

The mediastinal, bronchial, mesenteric, and retroperitoneal lymph glands appeared pale white on section and did not show any special enlargement.

The intestines were somewhat dilated and apparently rather atrophic. Microscopically, a very marked change was evident. The lymphoid elements were markedly hyperplastic and there were also evidences of extensive chronic inflammatory processes. The glands were largely degenerated, and in many places had disappeared, their places being taken by young fibrous tissue or aggregations of large, frequently phagocytic, mononuclear cells. There was practically no pigment deposit in this situation.

The stomach was slightly dilated, and its mucosa smooth and atrophic looking. Microscopically, there was considerable atrophy and degeneration of the glands, in parts also, small hyperplastic lymphoid aggregations, and also widespread subacute inflammatory processes.

The liver weighed 1600 grams, was very friable, and of a dark brownish color. It gave very rapid and very pronounced Prussian blue iron reaction. Microscopically, it showed a very widespread fatty degeneration, not being particularly localized in the central parts of the lobules, as it was in Case I. There was also a very considerable deposit of iron-containing pigment in the liver cells throughout the lobules, and also in all the tissues of the organ, including the lining cells of the vessels. In certain places the lining cells of the capillaries in the lobules were swollen, forming small groups, but no definite appearances of reformation of blood cells were observed.

The gall-bladder contained a small amount of orange bile. No stones. The bile passages were free.

The spleen, weighed 325 grams; it was slightly enlarged, very soft,

and of a dull red color. The Malpighian bodies were not evident. It also gave a very pronounced Prussian blue iron reaction. Microscopically, the Malpighian bodies were large and irregularly defined, evidently somewhat hyperplastic. The sinuses all appeared practically filled with nucleated cells. These cells were very frequently the seat of a deposit of hemosiderin pigment. Fairly frequently some small clumps of nucleated hemoglobin containing red cells of normoblastic, but more frequently of megaloblast, type could be seen adhering to the walls of the sinuses. It seems as if there were, then, some little regeneration of blood cells taking place in these sinuses from endothelial proliferation and specialization.

The kidneys were slightly enlarged, pale, flabby, and of a pale yellow, slightly brownish color. They gave typically in their cortical parts, a very bright Prussian blue reaction. Microscopically, there was a very extensive fatty degeneration, involving particularly the cells of the secreting tubules.

In none of these organs was there any amyloid change. The bladder and prostate were negative.

The pancreas also showed no abnormalities, except slight atrophy.

The bone marrow in the centre of the shaft of the femur was dark red in color. Microscopically, the erythroblastic and leukoblastic change was not so marked as in the first case, yet very largely the fat spaces had been replaced by aggregations of regenerating blood cells. There were in these places numerous megaloblasts and normoblasts, also frequent myelocytes in all stages of transition to polymorphs. In this case also coarsely eosinophilic cells could only very occasionally be observed.

The mastoids showed no signs of suppuration.

The large vessels at the base of the brain were very well preserved, and the membranes showed no abnormality grossly or microscopically.

The brain was slightly œdematous. It showed on minute examination no gross lesion. Microscopically, the cortex of the Rolandic and frontal areas, in the pieces examined, showed no special change, and the internal capsule, crura and pons likewise. In the lower part of the medulla there was a slight patchy degeneration in the lateral and posterior tracts. In the region of the decussation of the pyra-

mids it existed only in irregular streaks, and above this practically no changes could be seen. The nuclei of the medulla were not especially degenerated.

The membranes of the cord were in good condition, as also were the nerves and vessels related to it. There was no excess of fluid in the spaces surrounding the cord. The cord itself was firm and in a fairly good state of preservation. Grossly, it showed no deformity or local shrinkage, or softening, but there was on section a slightly darker appearance than normal of the posterior and lateral columns.

Fig. 9. The spinal cord in Case II, showing combined degeneration of the posterior and lateral tracts; the direct pyramidal tracts are also considerably degenerated.

Microscopically, it was evident that throughout practically the entire length of the cord there was a very extensive degeneration of the posterior and lateral columns (Fig. 9). This degeneration was most extensive in the lower cervical region, becoming less marked above this, and gradually also below it. In the sacral region it was only very slightly evident after the first segment. In all situations it was irregular, not being confined to any well circumscribed area, and not strictly adhering to the cord tracts. The posterior column lesion

was rather better defined and apparently of older standing than was the change in the lateral columns, also the lateral column lesion became less extensive and less complete in the lumbar region than the corresponding change in the posterior columns. There were, however, degenerative changes noticeable in the lateral columns as low as the lower lumbar region. Throughout the entire length of the degeneration in the posterior columns, and specially in the dorsal region, the outer part of the column of Burdach, for a narrow strip along the posterior tract was comparatively unaffected. The degeneration in the lateral columns did not exclusively affect the crossed pyramidal tract. The direct cerebellar and adjacent parts of Gowers' tract were generally irregularly involved.

The direct, or anterior, pyramidal tract was very irregularly affected, being degenerated for short areas on one or both sides.

The degeneration in all these situations, which was characteristically irregular, appeared as a disintegration of the nerve fibers with solution of the myelin sheaths. There was thus produced a vacuolated, somewhat reticulated, appearance. Even in the most degenerated areas some unaffected nerve fibrils remained, and many fibrils also had the appearance of a solid, homogeneous body, containing no central axon. There seemed to be no inflammatory reaction in these areas and relatively only a small amount of replacement gliosis. There were apparently no hemorrhages or inflammatory changes anywhere. The gray matter was intact throughout. Many of the ganglion cells showed some slight evidence of degeneration, probably postmortem in origin, and often were somewhat over-pigmented, but there were no evidences of inflammation nor of hemorrhage.

The vessels of the cord in general and in the degenerated areas showed no particular abnormality, although several of the small arteries did occasionally show a slight degree of hyaline degeneration. There was in no situation found any process of endoarteritis.

These two cases illustrate two of the types of nervous system involvement occurring in the course of pernicious anemia. In the first case, which had the longer and more pronounced history of anemia, the nervous symptoms were at a minimum, and the posterior columns of the cord, particularly in the cervical region, alone showed

degeneration, characteristically patchy in distribution. In the second case, the nervous involvement, particularly in the later stages, overshadowed the anemia. Here the spinal cord presented very extensive yet incomplete degeneration with slight replacement gliosis in the posterior columns, and also a similarly irregular but more diffuse degeneration in the lateral tracts, which, however, was a rather less complete and apparently a somewhat more recent process.

The nervous manifestations observed clinically in both cases did not quite correspond in severity with the extent of the pathological spinal cord lesions, a fact which has been repeatedly noted (Strümpell, Dinkler, etc.).

It bears repeating, however, that cases of combined sclerosis pass the neurologist without the gravity of the anemia which sometimes accompanies it being appreciated. It is also true that the internist overlooks the fact that in pernicious anemia changes may be taking place in the cord, which only delicate tests by a skilled neurologist can detect. Most of the records bear out this statement.

The occurrence of changes in the nervous system, particularly what has been termed pseudo-combined sclerosis, associated with pernicious anemia, has been very frequently and extensively described since the time of Lichtheim, in 1887, and has thus come to be a well recognized possible event. Such lesions in the spinal cord in pernicious anemia have been described by practically all observers, as an irregular degeneration of sclerosis in the posterior columns, with, in many cases, a similar associated process in the lateral, particularly pyramidal tracts. Kast and Alt, however, have described local changes in the medulla in leukemia, and Dana and others have noted localized areas in the spinal cord of softening from vascular obstruction.

The clinical symptom-complex of pseudo-combined sclerosis is well reviewed in the publications of Collier, Batten, and Russell (1900), and Siemerling (1909).

This combined tract degneration as the advanced stage of nervous involvement, and, at least, degenerative changes in the posterior columns, have been noted with identical appearance in a great variety of chronic, toxic, cachectic, or anemic conditions. Dana gives 10 per cent. as the number of cases described as combined sclerosis

which were due to pernicious anemia. Besides this, there have been reported cases dependent on chronic ergot poisoning, carcinoma, diabetes, septicemia, ulcerative endocarditis, pellagra, lathyrism, nephritis, malaria, shock, lead, arsenic, and phosphorous poisoning, Addison's disease, tuberculosis, syphilis, diphtheria, typhoid, influenza, scarlet fever, chronic jaundice, chronic alcoholism, leukemia, bothriocephalus anemia, after extirpation of the adrenals experimentally (Tizzoni), acute insanity, etc.[1] Such a list offers a strong evidence in support of a toxic factor as the primary agent in producing the tissue changes. Old age has also been ascribed as a cause of similar spinal cord degeneration, Sanders (1900), Noka (1906), and others having noted changes particularly in the posterior columns. Leyden discusses this problem of cord involvement in old age and concluded that it was a process secondary to some ganglion cell atrophy, rather than a primary white matter degeneration. Ribail traced the condition found in certain old subjects to a thickening of the membranes, with resulting local sclerosis, and Démange concluded that the spinal cord lesions in old age result from a thickening around and of the walls of vessels, which, however, causes appearances differing widely from any system of sclerosis. It might also be mentioned, although our observations are not sufficiently numerous to be conclusive, that of the cord lesions from four extremely old and very atrophied subjects who presented at autopsy absolutely no other lesion than extreme general atrophy and some little arteriosclerosis, none showed areas of degeneration anywhere, and, indeed, were remarkably and relatively well preserved. It must, then, be held that any toxic process, if sufficiently severe and prolonged, may cause a degeneration in the posterior tracts, or even the development of a widespread combined degeneration.

Clinically, from the records available, it seems impossible to associate the extent of the cord lesion with the degree of anemia. It seems, however, reasonable to infer that when the tissues are fed by the altered blood of these anemic states a condition analogous to ischemia exists, and at such times changes in the nervous system would be likely to begin or extend. It would seem, therefore, that

[1] For full list with exact reference see article by Camac and Milne, Amer. Jour. Med. Sci., October, 1910.

when the blood conditions are at their severest, the most critical neurological examination should be made and repeated at frequent intervals.

In the evolution of the literature of the spinal cord changes in pernicious anemia, several different pathological processes have been described as being the essential etiological factor. Thus, coalition of multiple small areas of hemorrhage to form a tract sclerosis was advocated by many of the earlier writers (Teichmuller, Minnich, von Noorden, etc.). Myelitis was the essential process according to Nonne. Boedecker and Juliusberger, Marie, Rothmann, etc., described it as endogenous, being the sequence of an involvement of the ganglion nerve cells. Thickening of the vessel walls, with resulting defective nutrition of the cord, was considered by Nonne, Minnich, and others. It has also been suggested by Schmaus, etc., that the immediate destruction of the medullary sheaths and degeneration of the neuraxons is dependent on lymph stasis, due to the impoverished condition of the blood and its excess in lymph elements. All these various conditions could not, for obvious reasons, be responsible for the appearances found in the cord in pernicious anemia, nor could any evidences of such processes be observed in either of our two cases. Excessive fatigue is also a very doubtful factor, as it has been shown that nerve fibrils are practically inexhaustible, and certainly less so than the ganglion cells or muscles. The process agreeing with the conclusions of most modern authors, appears to be that of a degeneration, with more or less replacement gliosis, and this accounts best for its irregular, imperfectly systemic, and incomplete character.

To account for the degeneration occurring especially in the posterior columns, Orr and Rows have shown that in tabetic conditions the degeneration is particularly marked at the point of entrance of the nerve roots. Also by injections of tetanus toxin and various bacterial emulsions into nerves they have demonstrated how the toxic agents ascend to the cord. They consider that the immunity of the nerves is due to the enveloping neurilemma and that only in the unprotected portion of the system where the nerve fibrils are contained in the cord can the toxins produce any effect. It is certainly, however, somewhat difficult to apply this to either of our cases; more-

over, in both of our cases, the posterior roots were not altered. It seems more natural to assume a greater vulnerability to degenerative processes in certain areas of the spinal cord than in others.

In connection with these cases it has to be, to some extent, considered just how far postmortem conditions can simulate any system lesion. These postmortem processes, however, do not produce the peculiar degenerative vacuolation nor the hyaline appearances of gliosis. In this connection the study of a series of such postmortem conditions in the cord at various intervals after removal from the body was undertaken with the result that system changes or appearances such as have been described were not observed.

In the consideration of the cavity formation in the lower dorsal region in Case I, there perhaps lies the one point of interest, which permits of these cases being put on record. The cavity, as has been noted, was situated on the left side of the cord, between the tenth dorsal and first lumbar segments, and occupied almost exclusively the gray matter, particularly of the anterior horn. This destruction and cavity formation corresponded almost entirely to a branch of the anterior spinal artery. This vessel supplies the greater part of the gray matter, while most of the rest of the cord is nourished by the pial vessels. It was apparently a thrombosis in one of the small veins, which accounted for all the œdematous separation of the tissues and the comparative absence, except where the cavity was largest, of any necrosis of tissue. This process probably was produced in the last few hours of life. It was difficult to be exact as to the duration of the process, as no clinical symptoms had been evident. The absence of clinical symptoms is explained by the location of the lesion and by the fact that the patient was comatose for some time before death.

Several examples of cases of thrombosis of the spinal cord vessels have been mentioned by various authors—Dana, Petrén, etc.—but the appearances, for the most part, have not been quite similar. These have been, in the majority of cases, of the nature of a hemorrhagic necrosis of the gray matter, particularly of the anterior horn. Experimentally, such conditions have also been produced by aseptic emboli, by Lamy, also Ehrlich and Brieger, Münzer and Wiener, Singer and Münzer, and Spronck have produced similar changes by

clamping the aorta in rabbits just behind the renal artery. Singer and Münzer showed in such conditions that areas of the posterior columns may become degenerated, but in our case the degeneration in the posterior tracts, besides being bilateral, was evidently of much older date than the cavity in the gray matter in the lower dorsal region.

Bulloch (1892) described in a case of pernicious anemia hyaline masses in the cord chiefly involving the anterior horns of the gray matter, and referred this to an exudation from the adjacent vessel. Henneberg (1899) described two cases of combined sclerosis in which there were found cavities in the spinal cord. In one case the cavity was central, and in the other it occupied the centre of one of the anterior horns. He considered thrombosis as the essential factor in their production.

The cavities in the spinal cord in syringomyelia, and the simple serous cysts which from time to time have been described in the cord and brain may, some of them at least, be possibly of similar origin. Again, certain cases of pernicious anemia have been described as terminating with fulminating and intense nervous symptoms, and in these the occurrence of multiple thrombi and resulting extensive cord destruction is very probable.

Had Case I of the two here reported survived, the final result would apparently have been one exactly like acute anterior poliomyelitis. It seems, moreover, peculiar that such conditions do not more frequently occur, particularly in various states of defective vitality or in the course of some general infective process.

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ON THE EFFICACY OF ANTIMONY-THIOGLYCOLLIC ACID COMPOUNDS IN THE TREATMENT OF EXPERIMENTAL TRYPANOSOMIASIS.

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Numerous efforts are being made to improve the treatment of the diseases caused by the flagellate protozoa known as *trypanosomes*, diseases which are among the most fatal and widespread of those known to medicine.

Among the best understood of the trypanosomic diseases are the sleeping sickness of human beings, which is rapidly extending its ravages in Africa; the tsetse-fly disease, or nagana, which occurs in the horse, mule, donkey, in cattle, and in other animals; *surra*, an Asiatic disease of the equidæ, of camels, and of cattle; the epizoötics of equines known as *mal de caderas*, *dourine*, and the Gambian horse disease, and also the epizoötic of the bovidæ known as *galziekte*, or gall-sickness.

A number of investigators have been fairly successful in the treatment of mice and rats which had been infected with the trypanosomes of these diseases, but the attempts to cure man and the larger animals, as horses, cattle, or even dogs, have not met with equal success. With the drugs at present at our disposal, the outlook for a permanent cure* in man is not hopeful if there are signs of a

* The difficulty of curing animals and men in the later stages is perhaps largely due to the fact that we here encounter stages of development in the reproductive cycle of the parasites which for one reason or another are probably not easily destroyed by the chemotherapeutic agents at our disposal. See, for example, Moore, Nierenstein, and Todd, Ann. of Trop. Med. and Parasit., i, p. 282; and Dutton, Todd, and Hanington; ibid., i, p. 20.

widespread invasion of parasites, particularly if the cerebrospinal system is so far involved that the spinal fluid, as obtained by lumbar puncture, gives histological evidence that the meninges have been invaded even though the parasites themselves may not be present in the specimen of fluid which is being examined.

Not only have the drugs now in use proved to be inefficient in sterilizing all of the tissues when once this widespread invasion obtains, but they have all developed untoward effects of so serious a nature that it has become necessary to search for new drugs which shall combine greater efficiency as parasiticides with fewer dangers to the host, or which shall possess even such minor elements of superiority as adaptability for subcutaneous administration or some other advantage which shall make them suitable for use as substitutes for those now in use. Our own work constitutes a contribution in this direction. The antimonials that we have employed in our experimental work are well adapted for subcutaneous or intravenous medication. It remains to be seen whether they have any advantages over the drugs now in use in the treatment of human beings, but we believe that our results are such as to warrant a trial of these drugs in the case of human trypanosomiasis as well as in the trypanosomic diseases of the domestic animals.

It is not our purpose to give a detailed history of therapeutic knowledge in regard to trypanosomic diseases. The publications of the Sleeping Sickness Bureau, the reports of Sleeping Sickness Commissions, the various special journals devoted to tropical diseases, and the various treatises on tropical medicine give full accounts of the brilliant work that has been done in this field since David Livingstone[1] in 1858 first suggested the use of arsenic in the tsetse-fly disease and tried it on a mare.

Various compounds of arsenic and of antimony and a number of dyestuffs have been brought forward as the result of the labor of laboratory workers and of physicians who have tested these substances in cases of sleeping sickness. As we are here more immediately concerned with compounds of antimony, we shall not enumerate the various arsenicals, dyestuffs and other drugs that have been or are being employed as trypanocidal agents, but shall refer the reader to the sources of knowledge already enumerated.[2]

The introduction* of certain salts of antimony into this branch of therapeutics by Plimmer and Thomson, acting upon a suggestion made to them by Cushny, was a distinct advance. These observers[3] made use of the antimonyl tartrates of potassium and sodium in the treatment of rats infected with nagana or surra, and were impressed with the quickness with which these drugs caused the disappearance of trypanosomes from the peripheral blood even when it was "swarming with the parasites." A dose of 0.35 c.c. of 1 per cent. solution caused their entire disappearance from the blood within half an hour. Recurrences, however, were observed in 4 out of 25 infected rats. Mesnil and Brimont,[4] who also and independently of Plimmer and Thomson made use of tartar emetic, obtained better results with this drug in the treatment of rats infected with *T. evansi* than with those infected with *T. brucei*, and also noted that this antimonial was trypanocidal for an atoxyl resistant strain of surra.

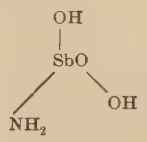
Uhlenhuth and Woithe[5] were less successful than Plimmer and Thomson with sodium antimonyl tartrate in the case of rats infected with *T. equiperdum*, but these authors, who were more especially concerned with atoxyl, speak of their experiments with the tartrate as "experiments of orientation" and advise the further study of antimonials especially in connection with atoxyl.

Breinl[6] was less successful with sodium antimonyl tartrate in the treatment of rats infected with a fairly virulent strain of *T. equiperdum* and stated that the local effects of the drug in rats were very severe, causing necrosis and sloughing, but nevertheless this investigator considered "that the introduction of another metal (antimony) belonging to the same group as arsenic is a further progressive step in the treatment of sleeping sickness and is moreover very suggestive."

* It would be more correct to speak of the *reintroduction* of this drug into the therapeutics of infectious diseases. It is of course well known that the *omne in omnibus* of Basil Valentine has had a wide use in the past in the treatment of agues, lobar pneumonia and other febrile diseases. In an essay published anonymously in London in 1747 (see Index Catalogue of the Surgeon-General's Library) by an author who styles himself "An Eminent Physician," "the celebrated drug" is vaunted on the title page as "one that is not only an effectual cure for the present distemper among the cattle but a preservative from their being infected." And in the body of the work it is stated that, "It (antimony) is esteemed and daily used by the farriers as a kind of panacea for horses. It cures those obstructions of the lungs that make them shortwinded, heals the scab and cutaneous diseases, and helps very much to bring an emaciated jade to good plight again."

From this time on progress in the study of the action of antimonials has been continuous and many advances have been made. Plimmer[7] and his associates have continued their studies on the behavior of various antimonials in rats and dogs and have also made important experiments "in order to find out where the trypanosomes rest during the period in which the peripheral blood is free from them after treatment with antimony." In conjunction with Bateman, Plimmer finds in rats that have been treated with antimony that trypanosomes live longest in the bone marrow and that the liver is also a place where these organisms find protection.

Breinl and Nierenstein[8] have recently extended our list of organic antimonials by preparing antimony compounds which are analogous to atoxyl. They have succeeded in preparing *p*, *m*, and *o*-amino-phenylstibinic acids. The action of these compounds was studied on animals infected with various strains of pathogenic trypanosomes. The *o*-compound was discarded after a few trials as impracticable. The *m*-compound caused marked swellings and abscesses and induced severe hemorrhagic nephritis and seems to have given only discouraging results. The authors point out that the corresponding *m*-amino-phenyl arsenic acid was found by Ehrlich also to be markedly inferior in therapeutic value to *p*-amino-phenyl arsenic acid (atoxyl). *P*-amino-phenyl-stibinic acid was administered in the



form of its sodium salt to rats, dogs and monkeys infected with *T. brucei*, *T. evansi* or *T. gambiense*, and the results showed that this compound is a fairly powderful trypanocide, though its action is not as rapid as that of sodium antimonyl tartrate. A trial of this compound is considered to be justifiable in patients suffering from sleeping sickness. It is also pointed out that a careful systematic examination of the urine is advisable inasmuch as kidney lesions are among the most pronounced results of antimony poisoning.

In this connection it may be noted that Kopke[9] has recently given a preliminary account of the action of this remedy in a case of sleep-

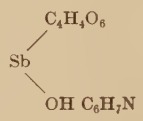
ing sickness in a human being in which atoxyl had absolutely no effect on the parasites, and found that it caused them to disappear promptly from the peripheral circulation. The hypodermic administration of the remedy induced only a small amount of local swelling but caused severe pain persisting for several days.

Thomson and Cushny[10] have tested a number of antimony compounds on nagana rats. Among those that were inefficient, impracticable, or valueless for one reason or another may be named diphenylstibinchloride ($(C_6H_5)_2SbCl_3H_2O$), potassium metantimoniate (SbO_2OK), a colloidal preparation of antimony oxide (Sb_2O_3) and a glyceride of antimony analogous to boroglyceride. Schlippe's salt, sodium sulphantimonate ($(NaS)_3SbS$), destroyed the trypanosomes in the rat, but induced very considerable local reaction, the results here being in agreement with those obtained with this salt in man by Broden and Rodhain.[11] Better results were obtained with sodium antimonyl malate and with solutions of ethylantimonyl tartrate prepared by Collie by heating freshly precipitated antimony oxide with ethyl tartrate to about 150° C. in sealed tubes. While tartrates and malates in the form of their sodium and potassium salt were found to be equally efficient as trypanocides, it was thought that the substitution of an alkyl radicle, as in ethylantimonyl tartrate, was attended with some advantage. Solutions of this compound, either as such or neutralized with ammonia induced no local reaction in rats and caused the trypanosomes to disappear from the peripheral blood within one or two hours. Thomson and Cushny conclude that in their experiments no other drug has given such favorable results. Out of 13 rats treated with a single full dose of this drug, 6 showed a recurrence on the fourteenth, sixteenth, twenty-second, twenty-sixth and twenty-ninth days. There was no recurrence in the 7 others. Of these 1 died of penumonia on the eighty-fourth day and 5 others from exposure to cold between the one hundred and thirty-fifth and one hundred and sixty-fifth day, leaving 1 survivor after two hundred and sixty days.

The strain of nagana here used was fatal to rats within six days after inoculation. As we shall see later a single full dose of a given drug is the more likely to be followed by a recurrence of the para-

sites in the blood the shorter the time that elapses between the injection and the usual time of death (in infected but untreated animals).

Laveran[11a] also has lately introduced a new antimonial into this field, Aniline antimonyl tartrate, which was first prepared by C. S. Evans who ascribes to it the formula



Laveran obtained such good results with this compound in the treatment of guinea-pigs infected with *T. evansi, T. gambiense, T. pecaudi* or *T. soudanense,* that he was induced to send some of the drug for trial in the field to Dr. A. Thiroux who has charge of a segregation village for sleeping sickness patients in Senegal near St. Thomas. The compound is less toxic than tartar emetic, and Thiroux finds that a intravenous injection of 0.150 gram suffices to drive the trypanosomes from the peripheral circulation. It also seems to have a more decided action on the central nervous system than atoxyl, for two individuals who were just entering upon the last or drowsy stage of the disease are reported to have greatly improved after an injection of 0.150 gram. It remains to be seen, as Laveran says, whether these satisfactory preliminary results will be found to be lasting.

It will be of interest to note what results have been obtained in the treatment of human trypanosomiasis by the antimonials which were first introduced. Manson[12] was the first to administer sodium antimonyl tartrate to a case of sleeping sickness and his experience led him to say "that antimony may have a therapeutic influence in trypanosomiasis, but the hypodermic injection of the sodium tartrate of antimony is impracticable." The injection causes intense irritation and pain.

Broden and Rodhain[13] were the first to use tartar emetic with encouraging results. These authors administered the drug intravenously in doses of 0.1 gram. A few of the patients thus treated responded with marked sweating and vomited two or three times. These symptoms disappeared after a few minutes. When this

quantity of the drug (0.1 gram) was given once a day for eight to ten days in succession, a large percentage of the patients showed signs of poisoning—they lost weight, had no appetite, and frequently complained of feeling ill. More than ten successive injections could not be tolerated. After the drug was discontinued the untoward effects that have been named rapidly disappeared.

G. Martin and Leboeuf and L. Martin and H. Darré have also administered tartar emetic (0.1 in 100 c.c.) in this way in numerous cases of sleeping sickness and have added to our knowledge in regard to its therapeutic limitations, and Thiroux has written a paper dealing with the untoward effects that are seen when tartar emetic is administered intravenously. It is pointed out by Thiroux[14] that tartar emetic should only be injected in very dilute solutions. Injections of 0.1 gram in 200 c.c. of fluid may be followed by a filiform pulse, vertigo, profuse perspiration, spasmodic cough, syncope or only momentary unconsciousness. These symptoms all pass off in a short time but the patient may feel more or less ill for a day. Thiroux seems to think that tartar emetic may have caused the death of one of his patients who had no lesion of the heart but nevertheless died from heart failure five days after having received intravenously a single dose (0.1 gram) of tartar emetic. This author now gives caffeine (0.02 gram) subcutaneously twenty minutes before injecting the tartar emetic, and states that his patients no longer evince untoward symptoms, especially if care be taken to inject very slowly.

It will thus be seen that the untoward symptoms that follow *immediately* upon the too rapid intravenous injection of tartar emetic may be avoided by the proper attention to details. Not so, however, with the damage that tartar emetic may inflict upon the kidneys, the liver or the gastric tract *when the drug is given in full doses for too long a period.* These more serious results can only be avoided by reducing the dose or by substituting from time to time for tartar emetic other antimonials or drugs that are less toxic.

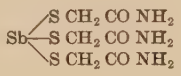
Martin, Leboeuf and Ringenbach[15] have tested the combined atoxyl-emetic treatment in advanced cases of sleeping sickness. Thirty-one patients of whom only one was in the first stage of the disease, were treated, with the result that ten died within a short time after treatment was begun. The conclusion of these investi-

gators is that the atoxyl-emetic combination does not succeed in staying the advance of the disease in patients who have reached the second stage and as such patients constitute the majority of cases seen amony the natives, the great desideratum is a rapid and easily applied cure for these cases.

It will thus be seen that the antimonials at present in use are limited in number, and like the arsenicals and other drugs that have been put to a searching practical test in human trypanosomiasis, they are of doubtful efficacy except in those cases which are still in the earliest stage of infection. Nevertheless the search for specifics against trypanosomes must go on, and even if the newer drugs have only a slightly less toxicity or some such advantage as greater penetrability for the central nervous system or better adaptability for subcutaneous administration, they will deserve to be tested in the trypanosomiasis of human beings or of the larger domestic animals under the conditions that prevail in the infected regions of tropical countries.

THIOGLYCOLLIC COMPOUNDS OF ANTIMONY.

During the past year one of us (A) has prepared the triamide of antimony thioglycollic acid.



This compound is obtained in the form of a thick syrup or semi-resinous body which is soluble in water in all proportions, is powerfully trypanocidal, and may be administered subcutaneously in solutions containing 0.010 gram to the cubic centimeter without signs of pain or local irritation. The compound tends to deposit a little sulphide of antimony on long standing and this is readily rumoved by filtration. *Only solutions that have been made perfectly clear by filtration should be injected subcutaneously or intravenously.* As in the case of antimonials in general only extremely dilute solutions, that is, only such as contain one-half or at most one milligram in the cubic centimeter, should be injected intravenously if

one wishes to avoid untoward effects like those that were cited in speaking of the clinical use of tartar emetic.

Preparation of $Sb\begin{cases} S\,CH_2\,CO\,NH_2 \\ S\,CH_2\,CO\,NH_2 \\ S\,CH_2\,CO\,NH_2 \end{cases}$

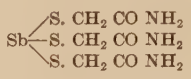
The first step in the preparation of this compound is the preparation of pure thioglycollic acid. For this we followed the directions given by Klason and Carlson[16] and prepared the crystalline barium salt ($Ba\,S\,CH_2COO + 3\,H_2O$) and from this obtained the free acid which was then purified by distillation under a barometric pressure of 14 to 16 mm. and at a temperature of 108° to 109° C. The preparation of the ethyl ester of thioglycollic acid is the next step, and here, too, we followed the directions of Klason.[17] The excess of alcohol is removed by distillation under diminished pressure and the ester is freed of the sulphuric acid employed in the esterification by shaking two or three times with distilled water, though some loss of material is here encountered in consequence of the partial solubility of the ester in water.

It was found that the ester readily dissolves antimony oxide and enters into combination with it, the products of the reaction being a heavy oil and a layer of water which floats on the surface of the oily or syrupy antimony compound. Quantitative experiments showed that six molecules of the ester will dissolve one molecule of Sb_2O_3 and the reaction may therefore be represented as follows:

$$Sb_2O_3 + 6\,HS\,CH_2\,COOC_2H_5 = 2\,Sb\begin{cases} S.\,CH_2\,COOC_2\,H_5 \\ S.\,CH_2\,COOC_2\,H_5 \\ S.\,CH_2\,COOC_2\,H_5 \end{cases}$$

The reaction takes place with evolution of heat. It has been our custom in the preparation of the new compound to use from 20 to 25 grams of the ethyl ester ($HS.\,CH_2\,COOC_2H_5$) and to add to it in portions of half a gram or so, a little more than the calculated quantity of the oxide, say 10 grams. The mixture is well shaken during the intervals of adding the oxide and if the heat of reaction itself is insufficient, extraneous heat may be applied to hasten the solution of the oxide. When all but a mere trace of the oxide, which is held in the form of an emulsion in the extruded water, has been

dissolved, the oily antimony compound is separated and cleared by filtration.* This compound is apparently not adapted for therapeutic purposes, as it is insoluble in water and as its solutions in oily menstrua induce pronounced local irritation. We have, therefore, changed this compound into the triamide:



To this end the antimony-ester compound is dissolved in absolute alcohol and ammonia is passed into the solution until the reaction is judged to be complete. At the first contact with ammonia the solution becomes turbid, the turbidity then gives place to a mass of slender prismatic crystals, and as the solution becomes warm these disappear and the newly formed amide settles out as a thick viscous mass at the bottom of the flask. At this point the flask is removed and a large excess of ether, which has been freed from peroxide, is added in order to throw out the amide which still remains in solution. After allowing the flask to stand for a few hours the supernatant fluid is removed and the triamide dried *in vacuo* over sulphuric acid and paraffine for the complete removal of adherent ammonia and alcohol. For purposes of analysis the compound may be further purified by solution in the smallest quantity of water, precipitated with alcohol and ether and again dried *in vacuo*. The amide as above prepared is, however, pure enough both for analytical and therapeutic purposes. When dried *in vacuo* it may be described as a colorless or slightly reddish semi-resinous compound which is soluble in water in all proportions with a neutral reaction and only slightly soluble in strong alcohol. The addition of the fixed alkalis to an aqueous solution decomposes this amide with deposition of antimony oxide and on standing exposed to light and air such solutions also deposit antimony sulphide.

In proof of the statement that the elementary composition of this compound must be represented by the formula $Sb\ (S.\ CH_2\ CONH_2)_3$ we append the following analytical data:

* On long standing in a tightly corked flask which is almost filled with the oil, clusters of glittering prismatic crystals separate out and a large part of the oil may be found after a few weeks to be transformed in these crystals.

I. 0.1686 gram triamide was boiled in a Kjeldahl flask with a sufficient quantity of a dilute solution of sodium hydroxide until all of the ammonia was driven off. Hydrochloric acid was then added in slight excess and the solution was again boiled until all traces of hydrogen sulphide were removed. Sodium bicarbonate in excess was then added and the solution was titrated with an approximately $\frac{N}{10}$ solution of iodine (1 c.c. = 0.0059 gram Sb.). 8.80 c.c. of this iodine solution was required for the completion of the reaction = 0.0516 gram Sb. = 30.61 per cent. Sb.

II. 0.3859 gram triamide was dissolved in water and treated with hydrogen sulphide, the Sb_2S_3 was collected, dried and found to weigh 0.1645 = 0.1175 gram Sb. = 30.53 per cent. Sb. The filtrate from the sulphide was evaporated to dryness and then analyzed for sulphur by the method of Carius, when it yielded 0.6822 gm. $BaSO_4$ = 0.0937 gram S = 24.34 per cent. S.

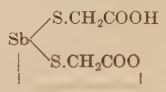
III. A nitrogen determination was made by boiling solutions of the amide with an excess of free alkali, collecting and estimating the liberated ammonia. 0.2502 gram amide yielded a quantity of ammonia which required 18.05 c.c. of $\frac{N}{10}$ acid for its neutralization = 0.02527 N. = 10.10 per cent. N. This analysis shows a

Summary of analyses	Theoretical requirements for $Sb(S.CH_2CO\,NH_2)^2$
Sb = 30.61 per cent.	Sb = 30.77 per cent.
30.53 per cent.	
S = 24.34 per cent.	S = 24.61 per cent.
N = 10.10 per cent.	N = 10.77 per cent.

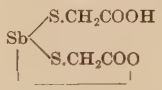
slight deficiency of nitrogen as compared with the theoretical requirements for our compound (10.77 per cent. N). The deficiency is accounted for by the fact that the amide had stood for a considerable time *in vacuo* over sulphuric acid at the time when this analysis was made. It slowly loses ammonia under these conditions, as was proved by the results of a second analysis a couple of weeks later when the nitrogen content had fallen to 9.64 per cent.

These data can leave no doubt that we are here dealing with an antimony compound of the composition above indicated. To the best of our knowledge the antimony ester $Sb\,(S.CH_2\,COOC_3H_5)_3$ and the triamide $Sb\,(S.CH_2\,CONH_2)_3$ furnish the first examples of the attachment of three radicles of thioglycollic acid to a single

atom of antimony. The analogous compound of arsenic* and thioglycollic acid [As $(S.CH_2COOH)_8$ is well known as having been prepared by Rosenheim and Davidsohn, but the only compound hitherto known as obtainable from thioglycollic acid and antimony oxide is antimony thioglycollic acid



in which one affinity of the antimony is satisfied by a replacement of the hydrogen in the carboxyl radicle of the acid. In the course of an investigation on the formation of complex salts Rosenheim and Davidsohn[18] described a compound which they supposed to have the composition $Sb(S.CH_2COOH)_3 \div 12\ H_2O$. The data given by these authors in support of this formula were very inadequate and unconvincing. On repeating their work, Klason and Carlson could only obtain the compound



and the proofs furnished by these investigators for the correctness of this formula are entirely convincing, as they give complete elementary analyses.

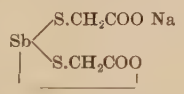
Ramberg[19] also states that he was unable to obtain the compound of Rosenheim and Davidsohn and is in agreement with Klason and Carlson that only the compound described by them can be obtained when thioglycollic acid is allowed to act upon antimony oxide. We may add that this has been our own experience also.

We would state in this connection that mercuric oxide was found to react even more readily and with greater evolution of heat than antimony oxide with the ester of thioglycollic acid. On subsequent

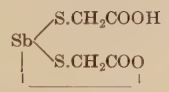
* Friedberger, (Berl. klin. Wochenschr. xiv, pp. 1714–1717, 1908) finds that a mixture of atoxyl and thioglycollic acid acquires an increase of trypanocidal power on standing and is then also effective in expelling the trypanosomes from the circulation of mice. Ehrlich mentions the compound of arsenic and thioglycollic acid, as $(S.\ CH_2\ COOH)_3$, as one of a series of compounds that are still effective in cases of atoxyl-resistance. Aside from these two instances we have found no writers who have made use of thioglycollic acid or of a thioglycollate of arsenic, and their work was only brought to our notice after our own experiments with the above antimonials were nearing completion.

treatment with ammonia a compound was obtained which was soluble with difficulty in water and which crystallized in the form of delicate slender prisms from its solutions in hot water. The low solubility of this compound discouraged further examination of it at this time, but we hope to continue our studies in this field in the near future. Anilides of both antimony and arseno-thioglycollic acid (As ($S.CH_2COOH_3$)) were also made but as these compounds also are insoluble in water we have not studied them any further.

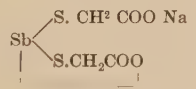
Sodium Antimony Thioglycollate.



This compound was made according to the directions of Klason and Carlson[20] and of L. Ramberg.[21] For the preparation of thioglycollic it is well to proceed according to the directions given by Klason and Carlson, and for the conversion of this into the antimony compound and the preparation of the sodium salt the directions of Ramberg should be followed. This writer ascribes to this salt the formula $NaC_4H_4O_4S_2Sb$, H_2O and states that it is obtained in the form of colorless prismatic crystals which are agglomerated into thick crusts and which are extremely soluble in water. For purposes of practical therapeutics it is sufficient to proceed as follows in the preparation of this salt. The pure crystalline acid



is suspended in a sufficient quantity of water and then converted into the sodium salt



by the addition of the calculated quantity of pure sodium carbonate, the solution is then concentrated (preferably under diminished pressure) until the solution becomes a thick syrup. Absolute alcohol is now added in small portions at a time until the salt is completely

precipitated. In this way a good yield of a partially crystalline white sodium salt is obtained which is sufficiently pure for all practical purposes.

Aqueous solutions are not entirely stable, although somewhat more so than those of the triamide. A trace of antimony sulphide is easily removable by filtration and it is advisable that solution should not be allowed to stand for any length of time.

RESULTS OF TREATMENT OF RATS

Sodium antimony thioglycollate and the triamide of antimony thioglycollic acid have been used in the treatment of white rats experimentally infected with various species of trypanosomes* as *T. brucei*, *T. evansi* (both surra of India and surra of Mauritius) or *T. equiperdum*. The nagana (*T. brucei*) strain used was exceedingly virulent, killing the rats in seventy-two to eighty-four hours regularly. The surra of India strain was practically just as virulent while that of Mauritius and that of dourine were much less virulent.

An attempt was made to protect rats against infection by administering sodium antimony thioglycollate twenty-four hours previous to the intraperitoneal inoculation with trypanosomes. No protection at all was afforded, each of the three animals so treated developing the disease in the usual time.

It was found, however, that the administration of either of these drugs subcutaneously at the time of the injection of the trypanosomes was always an absolute protection against infection as will be seen by a study of Table I. At different times four rats were so treated, two of which are still living after a period of four months without having shown any signs of infection, while the third died on the one hundred and sixtieth and the fourth died on the eighty-sixth day from pneumonia. At no time have trypanosomes been found in the blood of any of these rats.

* It gives us great pleasure to acknowledge our indebtedness to Professor F. G. Novy of the University of Michigan for sending us rats infected with nagana; and to Dr. Simon Flexner, Director of the Rockefeller Institute for Medical Research, for supplying us with strains of surra and dourine.

TABLE I.—Drug was administered at time of inoculation with the trypanosomes.

Drug given.	Disease.	Date of injection.	No. of rats injected	Dose.	Date of treatment.	Remarks.
				mg.		
Sodium antimony thioglycollate	Nagana	Jan. 11	1	3.5	Jan. 11	In good condition on July 1 (170 days).
	Nagana	Jan. 14	1	6	Jan. 14	Died of pneumonia on June 23, no trypanosomes could be found in the blood, two hours after death.
	Nagana	Jan. 17	2	3	Jan. 17	One of this pair died of pneumonia on the eighty-sixth day. No trypanosomes. The other is still living and is in good condition on July 1 (164 days).

TABLE II.—Treatment was commenced from eighteen to twenty-four hours after inoculation with nagana.

Drug given.	Date of infection.	No. infected.	Doses given.	Effect on trypanosomes.	Relapse	Death.	Remarks.
	Jan. 3	3	2 mg. on Jan. 4, 5, 6, 7,	disappeared	none	1 on 25th day	Accidentally crushed.
					none	1 on 26th day	No T. in blood. Cause of death unknown.
					none	....	Living after 178 days.
Sodium antimony thioglycollate	Jan. 4	2	1 mg. on Jan. 5, 6, 7, 8,	disappeared	none	1 on 16th day	Infection from bites of other rats.
					none	....	Living after 177 days.
	Jan. 4	2	3 mg.	disappeared	none	....	Living after 177 days.
					none	....	Living after 177 days.
	Jan. 4	2	1 mg. on Jan. 5, 7, 9, 11	disappeared	none	....	Living after 177 days.
					none	....	Living after 177 days.
Triamide	March 10	2	10	disappeared	none	....	Living after 112 days.
			8	disappeared	on 12th day	19th day	Died on 19th day.

The time elapsing between the date of inoculation and the beginning of treatment is the most important factor in determining the results obtained in treatment; the longer the period before the insti-

tution of treatment, the smaller the degree of success from the point of view of a radical cure; the shorter the period, the greater success.

Sodium antimony thioglycollate given any time within twenty-four hours after intraperitoneal inoculation furnished an absolute protection in every instance in which it was tried. Nine rats were given this drug subcutaneously in periods varying from eighteen to twenty-four hours after infection. The trypanosomes disappeared and in no instance returned as shown in Table II. Six of these rats are still living after periods of three to four months. One was killed accidentally, while another died on the twenty-sixth day of an unknown cause, but no trypanosomes were ever found in its blood.

The triamide was tried similarly on two rats. One had a relapse on the twelfth day and died on the nineteenth day, but the other is still living after two months and exhibits no evidence of the disease.

When the treatment is deferred until forty-eight hours after the injection is given, the trypanosomes in the blood are very numerous. Administration of either drug at this time will completely remove all the trypanosomes from the blood in one and one-half to two hours, the relapses will occur in nearly every instance unless repeated doses of the drug be administered. When a moderate dose of either preparation is given at the end of forty-eight hours and repeated on the fourth, sixth and eighth days after the infection, the blood remains free from trypanosomes for a period of two, three or four weeks, and in one instance the trypanosomes never returned. This rat weighing 80 grams, received 2 mg. of the sodium salt of antimony thioglycollate on December 23 and again on the 24th, and on January 3, 10, and 15. The rat is still alive on July 1, 1910, after one-hundred and ninety-one days and the trypanosomes have not reappeared.

The great majority of these rats have been subjected to an intermittent treatment, the drug being administered at intervals of from five to eight days. As a consequence many of these rats have shown no trypanosomes in the blood and have appeared perfectly normal over periods of months. Others have had relapses and have not been able to withstand the effects of repeated doses. Of this series of 22 rats treated with sodium antimony thioglycollate, 6 are still living; of the series of 26 rats treated with the triamide, 10 are still living.

When treatment is not instituted until the end of the third day or until terminal convulsions are present, the blood is found to be swarming with the parasites. In many of these cases there are present in the blood half as many parasites as there are red cells. The administration of the drug even when deferred until the terminal convulsions are present, or until the animal is too weak to stand, will cause a rapid disappearance of the trypanosomes from the blood. Rats, practically moribund at the time of its administration, have been observed standing on the edge of the water bowl, drinking, within two hours after the injection of the drug, and such rats have been kept alive and free from trypanosomes for weeks before they finally succumbed.

Fourty-four rats of this series (see Tables IV, IV*a* and IV*b*) have received treatment with the sodium salt at periods of three days or longer following infection. These rats have all been given the intermittent treatment and some have been thus kept for periods longer than three months without showing a relapse. When treatment is stopped, however, relapses occur at periods of from six and seven to fifteen and twenty days.

A few of these rats have received one dose of mercury but it was deemed wise to try the effect of these antimony salts themselves and so the mercury treatment was not continued.

Of the 44 rats treated in this series, 11 are still living, the period of survival ranging from forty to one hundred and fifty-two days.

Forty-nine rats of this series have been treated with the triamide (see Tables IV*c*, IV*d* and IV*e*) and of this number twenty are still living (July 1), the period of survival varying from forty-six to one hundred and thirty-one days. It would appear that of the two antimonials, triamide and sodium salt, the former is better tolerated over long periods of time.

TABLE III.—Treatment given forty-eight hours after inoculation.

Disease.	Drug given.	Date of infection.	Number treated.	Dose in mgs.	Dates of treatment.	Relapse.	Day of death.	Remarks.
Nagana	Sodium antimony thioglycollate	Dec. 21, 09	1	3	Dec. 23, 24; Jan. 3, 10, 15	none	....	Living after 191 days.
		Dec. 21, 09	1	2	Dec. 23, 24	none	16th day	Found in water bowl.
		Jan. 1, 10	3	2	Jan. 3, 5, 7, 9, 24, 27, 30	Relapse	30th day	
					Feb. 5, 12, 16, 21, 25			
					Mar. 4, 12, 18, 23, 28	Relapse	38th day	
					Apr. 2, 7, 11, 17	Relapse	8th day	Died day after last treatment.
		Jan. 3, 10	1	1	Jan. 5, 9, 16, 18, 24, 30 Feb. 3	18th day	37th day	No T. in blood at death.
		Jan. 3, 10	2	1	Jan. 5, 6, 7, 8, 15, 17, 19, 21	15th day	37th day	No T. in blood at death.
						18th day	39th day	No T. in blood at death.
		Jan. 17, 10	1	7	Jan. 19, 24, 31; Feb. 7	none	17th day	Died of the toxic effects of the drug.
		Jan. 17, 10	1	6	Jan. 19, 24, 30; Feb. 7, 12, 14	none	30th day	Died of the toxic effects of the drug.
		Jan. 22, 10	3	5 and 6	Jan. 24, 27, 30; Feb. 5, 14, 19, 24; Mar. 1	Relapse	42d day	
					3 mg. triamide Mar. 12	Relapse 21st day	49th day 50th day	Changed to triamide.
		May 18, 10	1	4	May 20	none	....	Living after 51 days.
		Apr. 20, 10	1	2	Apr. 22, 24, 29; May 9, 12, 19	none	....	Living after 71 days.
		Apr. 6, 10	1	4	Apr. 8, 11, 16, 21, 29. May 4, 11, 20	....	....	Living after 86 days.

TABLE III.—*Continued.*

Disease.	Drug given.	Date of infection.	Number treated.	Dose in mgs.	Dates of treatments.	Relapse.	Day of death.	Remarks.
Surra of India	Sodium antimony thioglycollate	Feb. 25, 10	1	2	Feb. 27, 1 mg. $HgCl_2$ Mar. 2	none	10th day	
		Mar. 22, 10	2	2 and 3	Mar. 24, 29; Apr. 5, 11, 16, 21, 28	none	38th day	
		Mar. 12, 10	1	2	Mar. 14, 16, 19, 22, 29; Apr. 5	none	31st day	
Surra of Mauritius	.....	Apr. 9, 10	1	2	Apr. 11, 15, 20, 24, 29			
					May 4, 11, 18, 24	none	....	Living after 82 days.
		Apr. 20, 10	1	2	Apr. 22, 24, 29; May 4, 12, 19	none	....	Living after 71 days.

Total number treated, 22. Number still living, 6.

TABLE III *a*.—Treatment given forty-eight hours after inoculation.

Disease.	Date of infection.	No.	Dose in mgs.	Dates of treatment.	Relapse	Day of death from date of infection.	Remarks.
Nagana	Feb. 24	2	6 and 10	Feb. 26, Mar. 7 (3 mg. $HgCl_2$, 2-28 and 3-5)	none none	12th day 17th day	No. T. in blood. No T. in blood.
	Mar. 10	3	4 and 5	Mar. 12, 14, 17, 20, 23, 29	....	18th day	Acidentally killed.
				Apr. 5, 12, 18, 24, 30; May 6, 13, 18, 23	.... May 18 23	....	Second rat escaped. Third is living after 112 days.
	Mar. 23	1	5	Mar. 25, 27; Apr. 8, 16, 21, 27	....	.....	Living after 99 days.
	Mar. 31	1	7	Apr. 2, 5, 8, 13, 19, 25, 29	none	33d day	
	Mar. 10	2	5, 7, 8	Mar. 12, 15, 19, 23, 29; Apr. 5, 12, 18	none	.....	Living 112 days.
				Apr. 24, 30; May 8, 16, 23	none	.....	Living 112 days.
	Apr. 11	1	5	Apr. 13, 16, 20, 24, 29; May 4, 13, 20	none	.....	Living after 80 days.
	Apr. 4	1	5	Apr. 6, 11, 14, 16 21	none	18th day	Died of the toxic effects of the drug.

TABLE III *a.—Continued.*

Disease.	Date of infection.	No.	Dose in mgs.	Dates of treatment.	Relapse.	Date of death from date of infection.	Remarks.
Nagana	May 11	1	4	May 13, 17, 19	none	.....	Living after 20 days.
	Mar. 12	1	5	Mar. 16, 19, 23, 29; Apr. 5, 9, 13	none	32d day	
Surra of India	Mar. 8	2	10	Mar. 10, 12 (5 mg.) 15, 20, 26 30	....	5th day	Overdose.
				Apr. 5, 12, 18, 24, 30; May 6, 12, 18, 24	none	.....	Living after 114 days.
	Mar. 10	2	8 and 10	Mar. 12, 15, 19, 23, 29 (5 and 6 mg.), Apr. 5, 11, 16, 22, 28 May 5, 12, 19	relapse	56th day	No T. in blood. Living after 112 days.
	Feb. 9	1	5	Feb. 11, 16, 24; Mar. 4, 10, 16, 23, 29 Apr. 5, 11, 17, 24, 30; May 6, 13, 19	none	.....	Living after 141 days.
	Mar. 26	3	3	Mar. 28, 31; Apr. 5, 8, 13, 24	....	35th day 24th day 29th day	
	Apr. 6	1	5	Apr. 8, 13, 16, 22, 28; May 4, 11	none	38th day	
Surra of Mauritius	Apr. 2	1	5	Apr. 4, 11, 16, 21, 28; May 2, 11	none	45th day	
	Apr. 22	1	2	Apr. 24, 30	none	11th day	
	Apr. 28	1	5	Apr. 30; May 6, 31	none	34th day	
Dourine	May 11	1	5	May 13, 15, 19, 24	none	.....	Living after 50 days.

Total number treated, 26. Number still living, 10.

TABLE IV.—Treatment not given until the end of the third day after infection or later. Drug used, sodium antimony thioglycollate.

Disease	Date of infection	Number treated	Dose in mgs.	Dates of treatment	Relapse.	No. of days rat lived	Remarks
Nagana	Dec. 19	1	3	Dec. 22, 24; Jan. 3, 10	none	22	Died of pneumonia No T. in blood
	Jan. 3	1	4	Jan. 6, 12, 19, 30; Feb. 4	Jan. 30	34	T. in blood
	Jan. 4	1	4	Jan. 7, 11, 15, 24, 30; Feb. 12, 20, 26; Mar. 4, 7	none	65	Given Hg. on 7th
	Jan. 4	1	5	Jan. 8, 11, 16, 24; Feb. 5, 14	Feb. 21	48	T. in blood
	Jan. 8	1	3.5	Jan. 11, 15, 18	none	21	No T. in blood
	Jan. 8	1	5	Jan. 11, 15, 18, 30; Feb. 7	none	39	No T. in blood
	Jan. 11	1	5	Jan. 14, 18, 24	none	17	No T. in blood
		1	6	Jan. 14, 18, 24, 30	none	28	No T. in blood
		1	7	Jan. 14, 30; Feb. 4, 7	Jan. 30	32	No T. in blood
	Jan. 14	2	5	Jan. 17, 20, 24, 31; Feb. 7, 12, 19	none Jan. 12	17 37	No T. in blood
	Jan. 17	2	7	Jan. 20, 24, 30; Feb. 5, 12, 21, 26; Mar. 5, 13, 20, 25	none several	43 70	No T. in blood No T. in blood
	Jan. 25	1	8.5	Jan. 28; Feb. 1, 5, 14, 25	Jan. 14	33	No T. in blood
	Jan. 28	2	10	Died next A.M. after treatment	....	4	
			8	Jan. 31; Feb. 3, 7, 14, 21, 26; Mar. 3, 9, 14, 22	Mar. 22	57	T. in blood at time of death
	Mar. 25	1	2.5	Mar. 28, 31; Apr. 5, 8, 14, 19, 24, 31	none	39	
	Apr. 8	1	3	Apr. 11, 14, 20, 24, 28; May 4	May 13	36	Died of trypanosomiasis
	Apr. 15	1	3	Apr. 18, 22	none	21	Chloroformed

TABLE IV *a*.—Treatment not given until the end of the third day after infection, or later. Drug used, sodium antimony thioglycollate.

Disease	Date of infection	Number treated	Dose	Dates of treatment	Relapse	No. of days rat lived	Remarks
Nagana	Apr. 6	1	4	Apr. 10, 11 (5 mg. tri-amid), 16, 21, 24; May 4, 11, 21	none	..	Living after 85 days
Surra of India	Jan. 30	1	5	5 mg. on Feb. 3, 10	none	11	
	Feb. 2	1	3	Feb. 5, 7, 9	none	29	Peritonitis
	Feb. 9	1	3	Feb. 12, 19. 24; Mar. 4	none	14	No T. in blood
	Feb. 18	1	7.5	Feb. 21	none	13	
	Apr. 8	1	3	Apr. 14, 19, 21, 27; May 5, 11, 18	none	49	Cause of death not known
	Mar. 28	1	8	Mar. 31, 5 (7 mg.), Apr. 9, 14, 18, 24 (5 mg.) 29; May 5, 19, 24	none	..	Living after 94 days
	Apr. 8	1	2	Apr. 11, 13, 18, 22, 28	none	24	
	Mar. 22	1	2 and 3	Mar. 25, 29; Apr. 5, 11, 16, 21, 28	none	39	
	Apr. 11	2	3	Apr. 14, 21, 30; May 5, 11, 19	none	32	
	Apr. 29	1	4	May 4	none	..	Living after 80 days
					none	..	Living after 63 days
Surra of Mauritius	Jan. 26	1	2.5	Feb. 3, 7, 14	none	17	
	Jan. 29	1	8	Feb. 7 (5 mg.) 14, 19, 28; Mar. 12 (2.5 mg.) 16, 18 (2 mg.), Apr. 5, 11, 15, 21, 29; May 6, 13, 20	none	..	Living after 152 days
	Feb. 1	1	4	Feb. 14, 19, 28; Mar. 2	none	36	No T. in blood
	Feb. 18	1	5	Feb. 21; Mar. 4, 16, 25, 30; Apr. 5, 11	Mar. 20	56	No T. in blood

TABLE IV *b*.—Treatment not given until the end of the third day after infection, or later. Drug used, sodium antimony thioglycollate.

Disease	Date of infection	Number treated	Dose in mgs.	Dates of treatment	Relapse	No. of days lived	Remarks
Surra of Mauritius	Mar. 28	1	4	Apr. 2, 5, 8, 16, 21, 29; May 4, 13, 19	none	..	Living after 94 days
	Feb. 18	1	5	Feb. 21; Mar. 4, 20, 25, 30; Apr. 5, 9	none	63	
	Apr. 24	1	4	Apr. 28; May 4	none	..	Living after 67 days
	Jan. 26	1	2	Feb. 9, 16, 24; Mar. 4, 12, 20, 28 Apr. 5, 13, 21, 30; May 12, 19, 27	Apr. 30 May 12 June 27 June 4	133	Died June 7, of pneumonia; had been paralyzed in hind legs for about 8 weeks before death. Penis diseased
Dourin	Mar. 30	2	3	Apr. 2, 5, 9, 28; May 6,13,20	none May 6	.. 45	Living after 91 days No T. at death
	Apr. 8	1	5	May 11, 15, 19, 24	....	..	Living after 63 days
	May 18	1	5	May 21	....	..	Living after 43 days
	May 6	1	5	May 12, 15, 19, 25	none	..	Cause of death not known
	May 21	1	6	May 24	none	21	Living after 40 days

TABLE IV *c*.—Treatment not given until the end of the third day after injection, or later. Drug used, triamide of antimony-thioglycollic acid.

Disease	Date of infection	Number treated	Dose in mgs.	Dates of treatment	Relapse	No. of days lived	Remarks
Nagana	Feb. 19	1	5	Feb. 24 ($HgCl_2$); Mar. 7, 14, 19, 23, 29	none	..	Living after 131 days
	Feb. 19	1	12	Apr. 5, 12, 19, 24, 30; May 5, 11, 18, 24; Feb. 25; Mar. 2 (7 mg.), 7, 10	none	24	No T. in blood
	Feb. 24	1	10	Mar. 1, 7	none	17	No T. in blood
	Feb. 19	1	5	Feb. 24; Mar. 2, 4, 7, 14, 23, 29; Apr. 4, 12, 19, 24	relapse	57	
	Feb. 21	1	7	Mar. 10, 15, 19, 26, 31; Apr. 5, 12, 16, 22, 30; May 6, 13, 20	none	..	Living after 129 days
	Mar. 4	2	7	Mar. 8, 14, 19, 27, 30; Apr. 5, 9, 11, 20, 28	none	29	No T. in blood
				May 4, 11, 18, 23, 31; June 7	none	100	Died of penumonia
				Mar. 31; Apr. 5, 18, 13 20, 24, 30	May 5	77	Died of pneumonia
	Mar. 28	2	7	May 5 11, 15, 21, 28; June 4, 9	May 16 28	76	Died of pneumonia
	Mar. 31	2	8–10	Apr. 7, 11, 16, 21, 26, 30; May 5, 11, 16, 21	Apr. 30 May 4	.. 14	Living after 91 days. Relapse
	Mar. 15	1	5	Mar. 18	none	10	Swollen face, cause of death not known
	Mar. 18	1	5	Mar. 21, 25	none	10	No T. in blood
	Apr. 13	1	5	Apr. 16, 21, 24, 29; May 5, 14	none	32	
	May 8	1	5	May 11, 17, 19	none	..	Living after 53 days
	May 2	1	6	May 6, 13, 16, 23	May 13 May 23	..	Living after 59 days
	May 5	1	6	May 8, 13, 23, 31; June 6, 10	May 18	..	Died June 22. Penis diseased, broncho pneumonia, no trypanosomes in blood immediately after death
	May 15	1	5	May 18, 20, 25	none	46	
Surra of India	Feb. 25	1	3	Feb. 28; Mar. 3	none	9	No T. in blood
	Feb. 27	1	3	Mar. 2, 4	none	10	No T. in blood

TABLE IV *d*.—Treatment not given until the end of the third day after injection, or later. Drug used, triamide of antimony-thioglycolic acid.

Disease	Date of infection	Number treated	Dose in mgs.	Dates of treatment	Relapse	No. of days lived	Remarks
Surra of India	Mar. 2	1	5	Mar. 5, 7 (3 mg. $HgCl_2$), 12	none	11	No T. in blood
	Mar. 5	1	5	Mar. 8, 12, 16, 21, 26; Apr. 5, 13, 27; May 2, 8	....	64	No T. in blood
	Mar. 20	1	6	Mar. 23, 26, 30; Apr. 7, 13, 22, 28; May 4, 12, 20	....	..	Living after 101 days
	Mar. 23	2	3 and 5	Mar. 26, 29; Apr. 5, 9, 15, 21, 29; May 5, 11, 19	none	43	Living after 109 days
	Mar. 14	1	6	Mar. 17, 21, 26, 31; Apr. 5, 11, 16, 20	Apr. 20	37	T. in blood
	Mar. 31	2	7 and 10	Apr. 3, 6, (5 to 8 mg.), 11, 16, 21, 28; May 4, 12, 19	none none	.. 30	Living after 91 days
	Apr. 3	2	10	Apr. 6, 9, 14, 21, 28; May 4, 13	....	38	
	Apr. 19	1	3	Apr. 22, 24, 29; May 5, 11, 15, 23; June 1	none May 21	47 46	Died of pneumonia
	May 1	1	8	May 4	none		Living after 61 days
Surra of Mauritius	Feb. 23	1	5	Feb. 27; Mar. 4	none	12	
	Mar. 20	1	3	Mar. 24, 28; Apr. 3, 5, 9, 15, 21, 28 May 5, 12, 14	none	..	Living after 101 days
	Mar. 24	2	5	Mar. 28, 31; Apr. 2, 5, 11, 16, 21, 29	none	..	Living after 97 days
				May 6, 13, 20	none	..	Living after 97 days

TABLE IV *e*.— Treatment not given until the end of the third day after injection, or later. Drug used, triamide of antimony-thioglycollic acid.

Disease	Date of infection	Number treated	Dose in mgs.	Dates of treatment	Relapse	No. of days lived	Remarks
Surra of Mauritius	Mar. 20	1	3	Mar. 24, 31; Apr. 5, 8, 13, 18, 24, 30; May 8, 15, 23	....	..	Living after 101 days
	Mar. 17	1	5	Mar. 20, 24, 29 Apr. 4, 12, 19, 30 May 8, 15	....	..	Living after 104 days
	Apr. 6	1	5	Apr. 9, 13, 16	none	17	Toxicity
	Apr. 14	1	5	Apr. 18, 23	none	17	Toxicity
	Apr. 17	1	5	Apr. 20, 24, 29; May 4, 12, 19	none	..	Living after 75 days
Dourine	Mar. 11	1	5	Mar. 14, 17, 23, 24; Apr. 5, 11, 16, 21, 27; May 2, 8, 15, 23	none	..	Living after 111 days
	Mar. 17	2	6	Mar. 30; Apr. 5, 9, 14, 20, 28	none	38	No T. in blood
				May 4, 12, 26	none	..	Living after 104 days
	Mar. 14	1	20	Mar. 17, 29; 15 mgs.; Apr. 5, 13, 20, 28; May 6, 14, 23	....	..	Living after 107 days
	Mar. 4	1	7	Mar. 8 (2 mg., $HgCl_2$), 10, 14, 19, 25, 30 (5 mg.); Apr. 5, 11, 17, 22, 30; May 8, 14, 21	....	..	Living after 117 days
	Feb. 9	1	10	Feb. 21; Mar. 4, 10, 17, 23, 29	Mar. 23	28	Paralysis. No T. in blood
	Mar. 1	1	5	Mar. 4, 7	none	8	Toxicity
	May 15	1	5	May 18, 23	none	..	Living after 46 days

DOSAGE

Sodium antimony thioglycollate can be administered to rats weighing 100 grams in 5 and 6 mg. doses, while 10 mg. can be given to a rat of 200 grams.

The triamide is less toxic, 8 to 10 mgs. being readily tolerated by a 100 gram rat and 20 mg. by a 200 gram rat.

These drugs may both be administered subcutaneously without evidence of irritation in 0.75 per cent. NaCl solution, the solutions containing anywhere from 5 to 10 mg. and the triamide as high as 15 mg. to each cubic centimeter. These solutions must be made up in small quantities for they do not keep well on standing. The sodium salt will remain clear at times for weeks but the triamide solution continuously precipitates antimony sulphide, which is, however, easily removed by filtration.

TREATMENT OF DOGS

Like other investigators in this field we have found dogs more susceptible to the toxic action of antimonials and arsenicals than smaller animals. It was determined by experiment that repeated doses larger than 8 mg. pro kg. of the sodium salt or 10 to 12 mg. pro kg. of the triamide, could not be tolerated. The toxic effects of these large doses repeated several times at intervals of a few days were an edematous bronchopneumonia, an enteritis of the hemorrhagic type and nephritis, especially when the treatment was prolonged. Prolonged treatment with somewhat smaller doses but too often repeated induces a type of chronic intoxication characterized by marked emaciation and fatty changes in the liver and other organs, and here too, we may meet with damages to the lungs, kidneys or gastric tract sufficient to account for death. In some cases even a single administration of the dose above named was not well tolerated.

We have settled on a dosage for subcutaneous administration in dogs of medium weight of 5 mg. pro kg. of the sodium salt.

The compounds used were made up so that 1 c.c. contained this quantity. Formation of abscess and sloughing (at the point of injection) occurred occasionally, but in the great majority of cases no local reaction whatever followed the administration of either compound. The triamide is somewhat less irritant than the sodium salt, and here the dose employed ranged between 5 and 10 or more mg. pro kg.

TABLE V.—Dogs treated with triamide.

Disease	Date of inoculation	Weight	Dose	Repetition	Relapse	Lived	Remarks
		Kg.	*Mg.*				
Nagana	Feb. 26	6.2	60	2	Positive	26	Trypanosomes in blood at time of death, but toxic effects of the drug also apparent
Nagana	Apr. 5		36	5	Negative	40	Died from the toxic effects of the drug. Cerebral symptoms pronounced
Nagana	Feb. 26	8.6	120	8	Positive	75	Had several relapses, cause of death not certainly known
Surra of India . .	Feb. 26	....	60	.....	Negative	18	Died from the toxic effects of the drug
Surra of India . .	Mar. 26	....	45	.....	Negative	13	Died from the toxic effects of the drug
Surra of India . .	Apr. 13	5	50	1	Negative	...	Living after 78 days
Surra of India . .	Apr. 16	....	50	5	Negative	54	Cause of death not known. Autopsy not made. No. of trypanosomes in blood on day of death
Surra of Mauritius .	Apr. 7	9.1	50	5	Negative		Living after 84 days

7 treated—2 living

The nagana strain used by us was exceedingly virulent for dogs. The parasites appeared in the peripheral circulation forty-eight to seventy-two hours after intraperitoneal inoculation and the infected animals died in from five to fourteen days. When the parasites of surra of India or of dourine were used, a longer times elapsed before

they appeared in the blood, but here also death occurred in from twelve to fifteen days. The surra of Mauritius was less virulent, requiring from two to three weeks to kill dogs infected with it.

We have made but one experiment to test the efficacy of our drugs in preventing infection and that was carried out as follows: A small dose of the sodium salt was given subcutaneously at the same time with the intraperitoneal inoculation with nagana. A dose of moderate size of the same salt was given on the fifth day following and again on the tenth day. In this way the disease was entirely prevented, no trypanosomes appeared in the blood and repeated subinoculations into rats have given only negative results. This animal is still living (July 1), and is in good condition after one hundred and sixty-seven days.

When treatment is delayed until the infection is well advanced and unmistakable symptoms of the disease are present, with trypanosomes in large numbers in the peripheral circulation, complete cure has not been effected by the administration of these antimonials. Their administration is followed, to be sure, by the immediate disappearance of the parasites from the peripheral circulation and by a decided improvement in the clinical condition. The dogs become lively and are apparently normal, but unless intermittent doses be administered, relapse occurs. Infected animals treated when apparently moribund are profoundly altered and apparently cured, but relapses are almost certain to occur. If repeated doses be administered at intervals of seven to ten days the relapse may be prevented but the animals will ultimately succumb to the toxic effects of the drug. This has also been the experience of others who have attempted to cure dogs with compounds of antimony[22] or of arsenic[23] when once the disease has become well established. In all, 9 dogs have been treated with the sodium salt, 4 of these being infected with nagana, the others with surra and dourine. One of these animals (with nagana) received one injection of the salt on the sixth day after inoculation, and died on the twenty-sixth day from the effects of a relapse. The others all died from the toxic effects of the drug and, with one exception, none of these had a return of the parasites in the blood. One animal of this series, weighing 5.5 kg. infected with surra of Mauritius, which was apparently cured sur-

vived for one hundred and seven days. The first injection was made on the twelfth day after the inoculation and at varying intervals thereafter the dose of 64 mg. was repeated five times. The parasites disappeared from the blood and never reappeared and the animal seemed to be perfectly normal in every respect. An injection of the triamide was now tried but with the result that cerebral symptoms appeared and that the animal died in convulsions four days later.

Treatment with the triamide gave results very similar to those described above. Of this series 2 animals are still living. Table V gives the data in relation to this series.

THE TREATMENT OF RABBITS.

All of our rabbits subjected to treatment were inoculated with the nagana strain elsewhere described. It kills rabbits in from twelve to twenty days when no therapeutic measures are instituted. The rabbit tolerates the antimonials here described better than the dog, toxic effects rarely following the administration of the sodium salt in doses of 10 mg. pro kg. or of the triamide in doses of 18 mg. pro kg.

In the treatment of rabbits as in the treatment of other animals, the time at which treatment is commenced is a factor of the greatest importance. One rabbit infected on January 17 and given 10 mg. of the sodium antimony thioglycollate at the same time has given no evidence of the development of the disease although one hundred and sixty-four days have elapsed. No trypanosomes are present in the blood and repeated subinoculations into rats have had negative results.

Another rabbit inoculated at the same time received 40 mg. of the sodium salt twenty-four hours later and has exactly the same history. The disease did not develop and the animal is perfectly normal one hundred and sixty-four days later.

Five other rabbits have been under treatment. One of these died on the fifty-fourth day from an extensive ulceration. This animal apparently had no relapse. Another is still living one hundred and thirty-six days after its infection, although it was not treated until

the twelfth day of the disease. This animal has received nine injections in all. No ulcerations are present though the animal has lost some in weight. No treatment has been given for three weeks and subinoculations into rats have proved negative in result. The accompanying table (Table VI) shows the details of these experiments.

TREATMENT OF A DONKEY.

On March 12, a donkey weighing 570 pounds was inoculated subcutaneously with 1 c.c. of blood from a three-day nagana rat. The blood of the donkey remained free from trypanosomes until March 17, on which day two to four parasites could be found in each field of the microscope. The animal's temperature rose from 98° F. on March 16 to 100.6° F. on the morning of March 17 and 102.4° F. on the same afternoon, it was depressed in spirits and showed a watery discharge from its eyes and nose.

At 3.30 P.M. on March 18 it was given 0.2 gram of sodium antimony thioglycollate intravenously.* Two hours later no trypanosomes could be discovered although several slides were examined. Its temperature gradually dropped, but on March 20, a large fluctuating tumor appeared between its front legs and this persisted for four or five days.

A second injection (0.5 gram) was administered on March 22, following which the temperature dropped to normal, where it continued to stay for six days. On March 28, coincident with the appearance of trypanosomes in the blood, the temperature rose to 100.9° F. Another dose (0.75 gram) of the drug was administered which was followed by a normal temperature on the following day.

The blood now remained free from parasites for twenty days during which period two injections (0.5 and 0.45 gram) were given and the animal appeared perfectly normal. A temperature varying from 100° to 102° F. was noted on two or three occasions, as may be seen by an examination of the accompanying chart. The animal was placed out in pasture for some time each day and was given a fair

* We take great pleasure in acknowledging our indebtedness to Dr. F. H. Mackie, State Veterinarian of Maryland, for his generous assistance in the care and treatment of this animal.

amount of exercise. Its appetite was good and it appeared in every way like a normal animal with the single exception that one of the hid legs became enormously swollen, being at one time nearly double the normal size. The swelling gradually subsided and one week later had entirely disappeared.

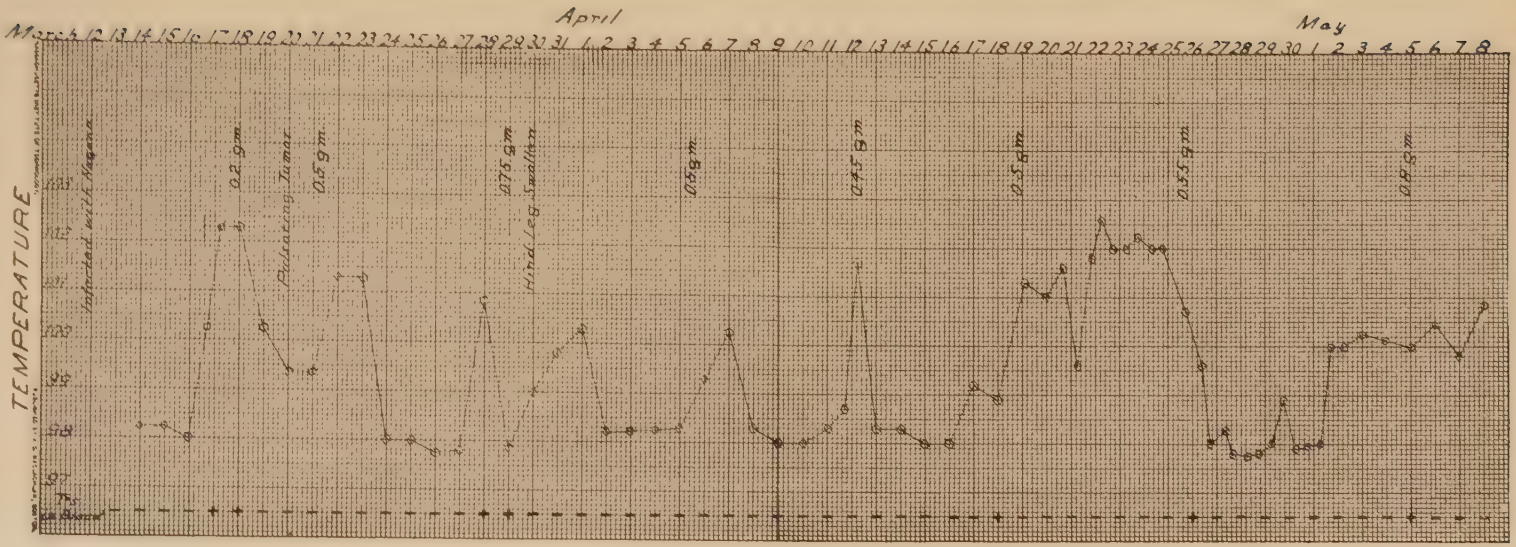
TABLE VI.—Treatment of Rabbits Infected with Nagana.

Date of infection	Dose	Weight kg.	Time of first treatment	Quantity of drug administered subcutaneously	Days lived	Remarks July 1, 1910
Jan. 17, '10	10 mg. Na salt	1.8	Same time	30 mg., three times. Last injection early in April	Living	Female, a week after giving birth to a litter of young, weighs 2.6 kg. In good condition after 164 days
Jan. 17, '10	20 mg. Na salt	3.0	Next day	40 mg., three times. Last injection early in April	Living Living	Male, now weighs 2.84 kg. In good condition after 164 days
Feb. 14, '10	40 mg. Triamide	2.0	Feb. 26	30 mg., six times at intervals of six days or more. Last dose (18 mg.) given on May 13	Living	Male, now weighs 1.73 kg. In good condition after 136 days
Feb. 14, '10	50 mg. Triamide	1.8	Feb. 26	.....	1	Died next day. No trypanosomes in blood. Subinoculation into rats negative
Mar. 31, '10	40 mg. Triamide	1.8	Mar. 15	40 mg., six times at intervals of a week	53	Death caused by ulceration of side penetrating into the peritoneal cavity
Mar. 1, '10	22 mg. Triamide	1.4	Mar. 15	.....	21	Died of antimony poisoning
Mar. 1, '10	35 mg. Triamide	2.1	Mar. 15	.....	18	Died of antimony poisoning

On April 18 the trypanosomes again made their appearance in the blood. A single injection (0.5 gram) drove them out again but the temperature remained between 102° and 103° F. The parasites again appeared in the peripheral circulation six days later.

CHART I

TREATMENT OF DONKEY WITH SODIUM ANTIMONYTHIOGLYCOLLATE



Another injection (0.55 gram) again caused their disappearance and a coincident drop in temperature. Their return eight days later was met with a rather too large dose (0.8) of the antimony preparation. Following this dose the animal appeared very sick, refused to eat and stood dejectedly in the corner and occasionally was found lying down. The breathing became very labored and difficult and on the fourth day following the last injection it died.

During the period of observation the urine was secured on two or three occasions and only the faintest trace of albumin could be detected. Up until death a fair quantity of urine was excreted and after death a full bladder was found. This sample was, however, unfortunately lost.

The blood count remained high throughout the disease, one week prior to death the leukocytes numbered 10,500 and the red cells 4,300,000 to the c.mm. During the disease the animal fell off considerably in weight but at death emaciation was not at all marked.

It will be seen from the accompanying chart that each injection successfully banished all parasites from the blood and that on many occasions the temperature following the injection became normal. The animal lived fifty-seven days and was in good condition until the time of the last injection three days prior to death.

Professor G. H. Whipple kindly performed the autopsy for us and permits us to publish the following report on the condition of the various organs. It will be seen that the death of the donkey was caused by the toxic action of the antimony and that here as in the case of dogs a lower dosage must be adhered to in order to avoid a fatal outcome. Further experiments with large animals must decide whether smaller doses than those here employed will prevent the reappearance of the parasites and yet do no harm to the host.

Thus far our result with the donkey and with dogs have not differed from those obtained by investigators who have preceeded us. Working with atoxyl, Uhlenhuth and Woithe[23] state that horses and dogs cannot tolerate the amounts of this drug which must be administered in order to destroy the parasites in their tissues. Moore, Nierenstein and Todd[24] were diappointed when they applied to donkeys inoculated with nagana their atoxyl-mercury treatment, a treatment which had been so successful in the case of rats. Not one

of a considerable number of donkeys could be cured by their method. So too, Breinl and Nierenstein[25] found that arsenophenylglycin was not tolerated either by the donkey or the horse inoculated with nagana. Schilling and Jaffe[26] also found that the horse cannot withstand the effects of this arsenical when administered intravenously or intraperitoneally in a total quantity of 0.06 gram pro kg. in two days.

Holmes[27] claims that arsenious acid is a specific for surra in horses. According to this investigator, Lingard, Bruce and others who were the first to try arsenic, met with failure because they attempted a continuous treatment with small doses. Holmes states that arsenious acid should be given in full subtoxic doses at intervals and not in continuous daily dosage and this method, he declares, has led to a number of cures of surra.

Taken as a whole the literature on the trypanosomiases of the equidæ and bovidæ contains but few instances of successful treatment and it is evidently of the greatest economic importance that further advances should be made in this branch of therapeutics.

AUTOPSY REPORT BY PROFESSOR G. H. WHIPPLE.

"The autopsy was performed twenty-six or twenty-eight hours after death and all the viscera showed more or less postmortem changes, particularly the intestines and the liver. The heart showed nothing of interest. Both lungs were very abnormal and presented an identical appearance which, however, was more marked in the left than in the right lung. The lung tissue in gross was a deep reddish purple color, rather flabby, but voluminous and very heavy. The bronchi contained a frothy serum. The cut section showed a very moist, purplish lung tissue, with a few indefinite areas which appeared to be consolidated, but the striking thing was the edema and the congestion.*

"Microscopic section showed an extreme grade of edema. The

* Note by the authors: That antimony will cause this change in the lungs has long been known. It appears that Magendie first speaks of it as a hépatisation "pulmonaire" in his treatise entitled, De l'influence de l'émétique sur l'homme et sur les animaux—as we gather from Paraban's Thesis, Nancy, 1875.

alveoli being full of an albuminous coagulum, as well as considerable blood in the alveoli, and all the capillaries were greatly engorged with blood. There were a few indefinite, very small patches of bronchopneumonia.

"The spleen was of normal size or possibly even smaller than normal. It was very flabby, and on section presented a dark purplish color which was blackened in places by the postmortem change.

"The liver was not enlarged and was very soft and flabby showing advanced postmortem change. Microscopic section showed no fatty degeneration and apparently a little increase in pigment. Postmortem digestion makes the picture rather obscure.

"The intestines were examined, but postmortem digestion was so advanced that examination was of practically no value.

"The kidneys were large, and the surface speckled over with large and small ecchymoses. Section showed a very thick cortex streaked with the same areas of hemorrhage. The tissue was very moist and boggy feeling.

"*Microscopic sections.* There was a certain amount of chronic diffuse nephritis with increase in connective tissue in all parts of the cortex, but the striking thing was the acute condition. The interstitial tissue everywhere was very edematous and full of wandering cells, especially polymorphonuclear leukocytes. . . . All parts of the kidney were more or less involved in the acute change, and the nephritis was of an extreme grade.

"*Anatomical Diagnosis.* Acute hemorrhagic nephritis; edema, congestion and bronchopneumonia of lungs; postmortem digestion of viscera."

THE DEVELOPMENT OF RESISTANCE IN TRYPANOSOMES TO ANTIMONY THIOGLYCOLLATE.

That trypanosomes may develop a pronounced and an inheritable resistance to certain drugs was first clearly established in Ehrlich's laboratory in the researches of Franke and Röhl[28] on trypan red. Since then it has been shown by Ehrlich and his pupils and by other investigators that resistance is developed in the course

of treatment with various arsenicals and dyestuffs, as trypan red and trypan blue, and lately Kopke[29] has described a case of sleeping sickness in which the trypanosomes were no longer affected by atoxyl.

Mesnil and Brimont[30] have observed that a surra of Mauritius strain which was atoxyl resistant in mice, rapidly acquired a similar tolerance for tartar emetic. The fifth injection of tartar emetic into mice infected with this strain was without effect on the parasites and when these were transferred to other mice they were found to retain their resistance to the drug. Even when the drug was given in the highest possible dose (0.40 to 0.45 mg. to 20 grams of body weight) it had not the slightest influence on the course of the infection.

The antimonials used by us do not readily cause the appearance of a drug-resistant strain. We have hitherto failed entirely in our efforts to obtain a nagana strain which should be resistant to thioglycollates of antimony. We note also that Mesnil and Brimont were less successful in obtaining antimony-resistance with nagana than with surra and that here they began their work with a strain which was already resistant to atoxyl. Even when in a few cases of nagana in mice the parasites were no longer destroyed by tartar emetic, these authors observed that on transference to fresh mice the strain again showed its former sensitiveness to the drug.

The following instance will illustrate the difficulty of obtaining a strain which is resistant to the antimonials employed by us. A rat infected with nagana was subjected to symptomatic treatment, a small dose of sodium antimony thioglycollate being administered at each reappearance of the parasites. In this way the rat was kept alive for one hundred and eight days and died on the day following the last injection of the antimony, being apparently worn out by the combined effects of the repeated injections and the recurrences of the disease. No sign of drug resistance could be detected, although the rat had received nineteen injections in all, the trypanosomes always disappeared promptly after each injection of the drug and the intervals between the relapses did not become shorter, the blood being free from trypanosomes for six days prior to the last injection (a period somewhat longer than the usual interval). A further attempt was made to develop resistance by transfer of the trypano-

somes from this rat to others. At various times nine rats were inoculated with this strain and treated as before. No resistance has developed. Three of these rats are still living and in them the parasites respond to treatment as readily as in rats inoculated with the untreated strain of nagana.

TABLE VII.—Experiments to obtain an antimony-thioglycollate-resistant strain in rats.

Drug	Date of infection	Number treated	Dose in mgs.	Date of treatment	Number of relapses	Number of days rat lived	Remarks
Sodium antimony thioglycollate	Apr. 1	2	5	Apr. 4, 7, 11, 16, 21, 25, 30; May 5, 11, 16, 21	3	(1) 15	One living after 90 days
	Mar. 13	2	2–5	Mar. 17, 25, 28; Apr, 5, 8, 15, 21, 28; May 4, 13, 20	one Mar. 28	(1) 20	One living after 109 days
	Mar. 17	1	3	Mar. 22, 28; Apr. 7	none	20	
		1	5	Apr. 13, 16, 21	none	12	Death due to the toxic effects of the drug
	Apr. 17	1	2	Apr. 22, 24, 25; May 5, 11	one May 5	25	
Triamide of antimony thiglycollate acid	Apr. 4	1	5	Apr. 7, 9, 15, 18, 24, 30; May 13, 23	one May 23	30	
	Apr. 7	1	5	Apr. 9, 13, 18, 24	....	....	Living after 54 days

TABLE VII *a*.—Experiments to produce resistance in T. brucci after passage through a donkey.

Drug	Date of infection	Number treated	Dose in mgs.	Date of treatment	Number of relapses	Number of days rat lived	Remarks
Sodium antimony thioglycollate	Apr. 27	1	5	May 3, 9, 11, 16, 19, 24	5	..	Living after 64 days
	May 9	1	5	May 11, 20	1	..	Living after 53 days
	May 11	1	3	May 14, 20	2	13	
	May 14	1	5	May 16, 20	..	9	Killed by other rats
	May 16	1	7	May 19, 21			
	May 19	1	5	May 21			

It will be seen, therefore, that we have been unable thus far to secure a strain resistant to our antimonials in cases in which rats alone have been used as animals of passage during the time of treatment.

The strain of nagana which was recovered from the donkey on its last relapse and which had been subjected in that animal to intermittent treatment with our antimonials has, however, shown some evidences of a greater resistance to antimony. Table VII*a* contains the data relating to this strain and an examination of it will show that relapses occur somewhat earlier and are more numerous than with the untreated nagana strain. In the case of one rat (rat on May 11) in this series a point was reached in which the second injection of the antimonial was powerless to free the blood parasites. Inoculation of a fresh rat with blood from the heart of this rat failed to infect, so that we can not know whether the hereditary characteristic had been acquired.* Our work on this point may be summed up in the statement that resistance has not been noted in the prolonged treatment of any *single* species of animals infected with nagana and that the only phenomena suggesting tolerance have been encountered in the strain which was subjected to treatment *in two different hosts, the donkey and the rat.*

CONCLUSIONS.

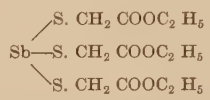
1. A new compound of antimony, the triamide of antimony thioglycollic acid,

$$\begin{array}{l} \quad\;\; \diagup \mathrm{S.\,CH_2\,CO\,NH_2} \\ \mathrm{Sb}\text{—}\mathrm{S.\,CH_2\,CO\,NH_2} \\ \quad\;\; \diagdown \mathrm{S.\,CH_2\,CO\,NH_2} \end{array}$$

has been prepared and found to be well adapted for subcutaneous and intravenous injections under the conditions stated in the body of this paper.

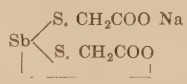
* Note under date of July 1. Since the above table was completed we have again found a rat inoculated with this donkey strain in whose case our sodium salt was unable, in a second dose, to drive the parasites from the blood. Subinoculation was effective in this case, *but no evidence of increased resistance could be found in the rats of passage.* Our results with rats are therefore to be placed by the side of those obtained by Mesnil and Brimont with mice, in which case also an occasional resistance did not become hereditary.

2. A new antimony-thioglycollic ester, having the composition represented by the formula,



has also been prepared, but this substance apears to be little suited to therapeutic purposes on account of its low solubility in water.

3. Sodium antimony thioglycollate,



was prepared according to the directions of Klason and Carlson and of Ramberg and was found to be well adapted for therapeutic purposes under the conditions stated in our paper.

4. This salt and the above named triamide have been tested in regard to their efficacy as trypanocidal agents in several series of inoculated rats, rabbits, and dogs. The trypanosomes employed were highly virulent strains of *T. bruccei* and *T. evansi* and somewhat less virulent strains of *T. epuiperdum* and *T. evansi* (surra of Mauritius). Only one large animal, a donkey, inoculated with *T. brucei* was subjected to treatment.

Our results in the way of treatment compare so favorably with those obtained by others in the use of the antimonials or arsenicals of the day in experimental trypanosomiasis that a trial of the antimony thioglycollates in human trypanosomiasis and in the trypanosomic diseases of the larger animals would seem to be warranted. In the case of the equidæ and bovidæ these drugs may be found to be of service as prophylactic agents during periods of exposure to infection in traversing a "fly region." Their relatively low cost and their small ability to induce drug-resistance in trypanosomes are factors worthy of consideration in this connection. It is not claimed that these antimonials are more efficacious in the long run as therapeutic agents than those hitherto used, but it is certainly worth while to enlarge the number of trypanocidal drugs, especially if their toxicity is less marked than that of their predecessors or if they are better adapted for subcutaneous injection.

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MAR
1911

HEART BLOCK WITH AN INDICATION OF GENUINE HEMISYSTOLE.

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AND

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The case of heart block which furnished the basis for the observations which we wish to report was not of such exceptional character that a separate publication of the clinical features would be of value; but the numerous tracings which were obtained furnished some interesting information, and by lucky chance one of these proved of unusual importance in throwing some light on the possibility of true hemisystole. We shall give only the outlines of the history and clinical aspects of the case and then proceed to the discussion of the more interesting features.

The patient was an Italian, aged thirty-nine years, a cabinet maker, and married. Three years ago pains in the epigastrium occurred. One year ago he had a severe attack of the same pain with an attack of syncope, but noticed nothing wrong with his heart. He had a fainting attack in August, 1908. Ten days before admission to the University Hospital he had epigastric pain, and was in bed for a few days. On returning to work the pain recurred at once, and he then noticed that it came with each beat of the heart and that the heart was beating very slowly. He went home, where he had several attacks of faintness, vertigo, and vomiting.

When twenty-three years old he had a suppurating bubo and a sore on the penis. No secondaries followed, but after leaving the hospital where he went for treatment several of his teeth fell out. He has four living healthy children; his wife had one miscarriage

before the four children were born. He has always been a healthy man, although he has not felt quite so well during the last three years. He has some pain along the edge of the tibiæ, especially in winter. The Wassermann reaction was positive.

The heart was enlarged one and one-half inches to the right of the sternum, but not beyond the left midclavicular line. A long systolic murmur was heard, and a dull second sound. When admitted, on February 5, 1910, at 6.30 P.M., the pulse rate was 62. The next morning it was 76, but it rapidly fell to 22 by noon, and did not rise above 34 until 6 A.M. on February 9.

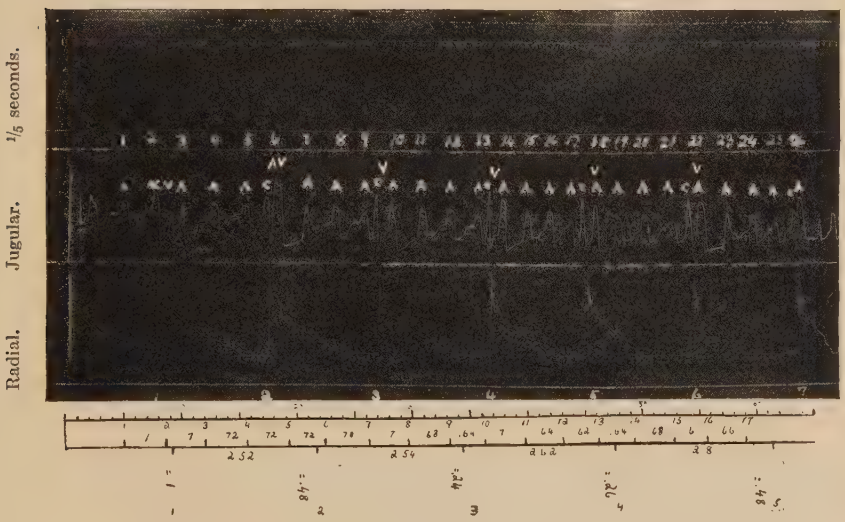

FIG. 1.—Tracing made February 6, 1910. Complete block.

The features that we wish to discuss are the following:

1. That although for a time complete block existed and later partial heart block, during the patient's stay in the hospital no Stokes-Adams syndrome was present.

2. That the complete block, after the administration of atropine, promptly changed to an incomplete block with a 3 to 1 rhythm, then to a 2 to 1 rhythm, and later to a normal rhythm.

3. That the 2 to 1 rhythm and the normal rhythm for a time alternated one with the other, and a number of tracings were ob-

tained showing this change while the tracings were actually being made.

4. That it furnished indications of genuine hemisystole during the transition of the normal rhythm to a 2 to 1 rhythm.

5. That from this same tracing it could be demonstrated that the origin of the *c* wave is the right ventricular contraction, rather than the carotid pulsation.

6. That the *a-c* interval is longer in such cases as this during normal rhythm, while it may be normal in length during partial block.

7. That the auricular rate becomes faster when the normal rhythm changes to a 2 to 1 rhythm, and slower when the opposite change occurs.

8. That explanations were suggested for the increased or decreased auricular rate during block and normal rhythm, and for the irregular ventricular rhythm during complete block.

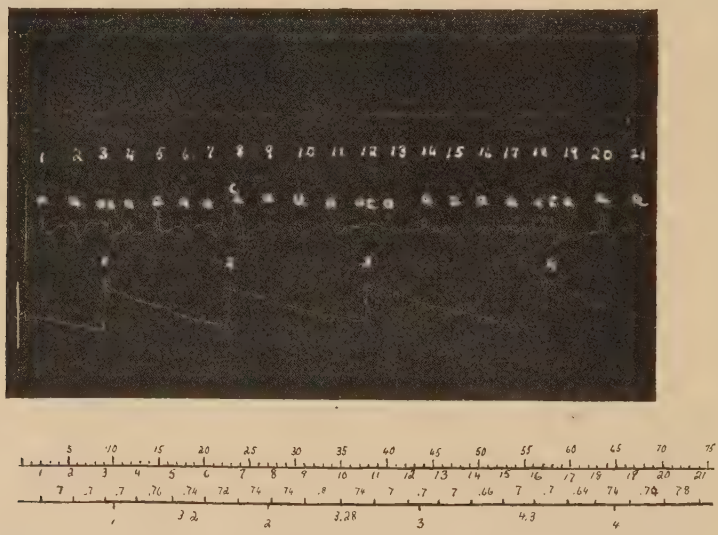

FIG. 2.—February 8, 1910. Before atropine was given. Complete block. Irregular ventricular action.

1. A study of tracings 1, 2, and 3, made on February 6 and 8, shows that the block was complete, and that during this time the radial pulse fell as low as 17 to the minute, and pauses were noted

between ventricular contractions of as much as 5.4 seconds. Several times 7 auricular contractions were observed between 2 ventricular ones, and yet not the slightest evidence of any Stokes-Adams syndrome was noted during the patient's stay in the hospital. During the phase of complete block the average ventricular rate from 35 measurements taken from 8 different tracings was 19.2 per minute, while the average auricular rate from 174 measurements was 80.7 per minute, a little more than four times as many to the minute.

2. A study of tracings 2 and 3, made at 1.30 P.M. on February 8, shows a complete block at that hour, and tracing 4, made 4 hours later after two hypodermic injections of atropine had been given —one at 1.30, of $\frac{1}{100}$ grain, and another at 4.30 of $\frac{1}{75}$ grain— shows that the complete block has changed to an incomplete one with a 3 to 1 rhythm. In tracing 4 the auricle was beating about 81 times per minute and the ventricle 27. Atropine was then given by the mouth every third hour, $\frac{1}{200}$ grain for two days, then withheld for four days, and then given again for a week. Tracings on the ninth day after the change from complete block to incomplete block, with a 3 to 1 ryhthm, showed a 2 to 1 rhythm, and thereafter up to the present date the tracings have shown either a 2 to 1 rhythm or no block at all. He has apparently had no return of the complete block since the two hypodermic injections of atropine on February 8.

3. Headings 3, 4, and 5 can be well considered together. On examining tracing 5 it will be observed that the normal rhythm changes suddenly to a 2 to 1 rhythm, brought on possibly by a deep breath that the patient had taken about seven seconds before, though more probably coming on spontaneously, as at this time the 2 to 1 rhythm and the normal rhythms frequently alternated. It will be seen that the first six *a* waves are followed, as they should be, by a *c* wave and accompanied by a wave in the radial tracing, but that the seventh *a* wave is not followed by a *c* wave, although accompanied in the radial by a wave exactly like the preceding one. The eighth *a* wave is followed by a *c* wave and accompanied by a wave in the radial, the ninth *a* wave is not followed by a *c* wave and is not accompanied by a wave in the radial, and from here on the 2 to 1 rhythm which has been started persists. Now, how are we to explain why the seventh *a* wave is

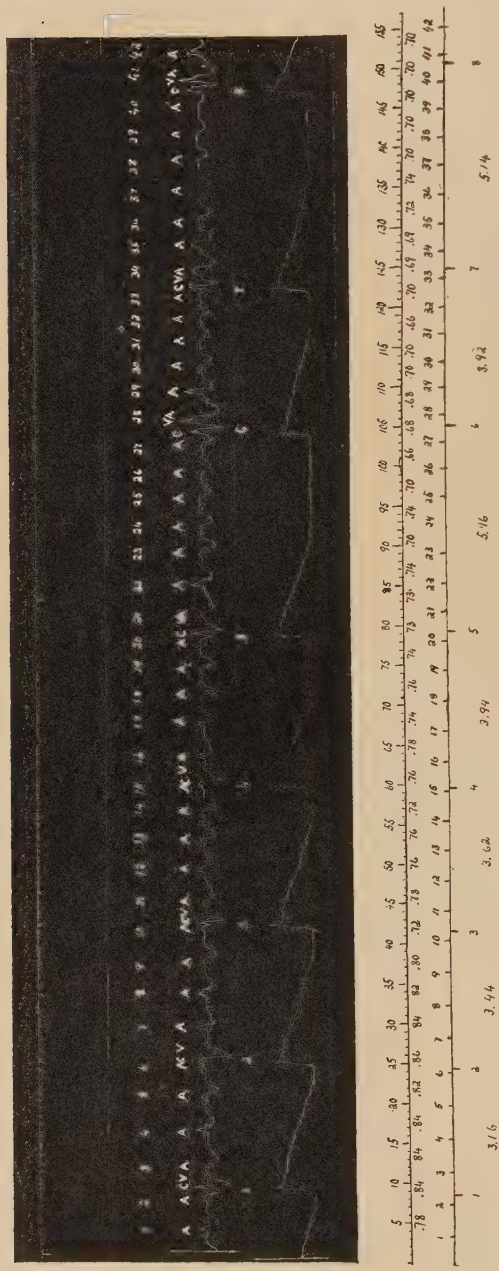

FIG. 3.—February 8, 1910. Before atropine. Complete block. Irregular ventricular action.

not followed by a *c* wave, although accompanied by a wave in the radial tracing? There being an *a* wave shows that the right auricle contracted, and there being a wave in the radial shows that the left ventricle contracted following the auricular contraction, but why is there no *c* wave? If the *c* wave is caused largely by the carotid artery, we should here in this case have a *c* wave, because, judging from the radial, the left ventricle contracted with its customary

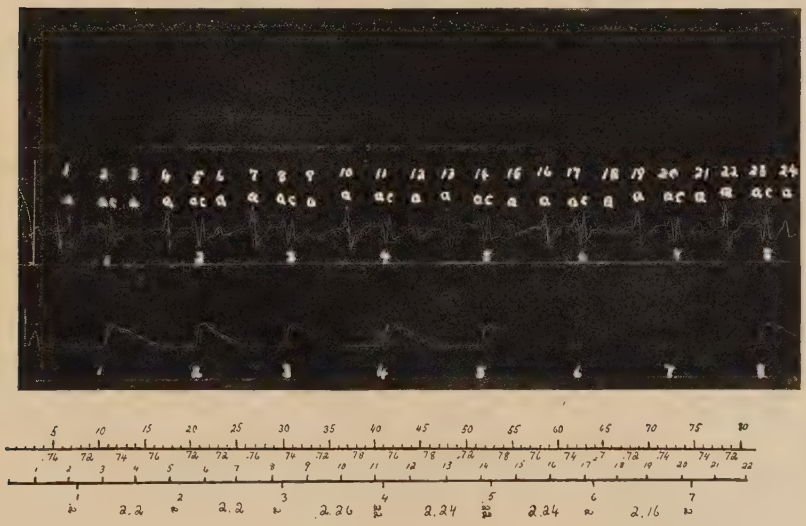

FIG. 4.—February 8, 1910. After atropine had been given. Incomplete block with 3 to 1 rhythm. *a-c* interval usually normal.

strength and at the proper time. Therefore, it seems to us that the *c* wave cannot be due to the carotid, but must be due to the right ventricle, and that in this particular instance the right ventricle did not contract or contracted feebly, although the left did contract normally. Coming as this did just before the institution of the 2 to 1 rhythm, it certainly suggests that the right ventricle ceased first, and then the left ventricle followed suit, and that then a perfect 2 to 1 rhythm resulted. This would seem to prove that one ventricle can contract normally while at the same time the other ventricle either contracts very feebly or not at all. Probably it would be unwise from this single observation to say that in this particular case the division of the bundle of His going to the right ventricle was more

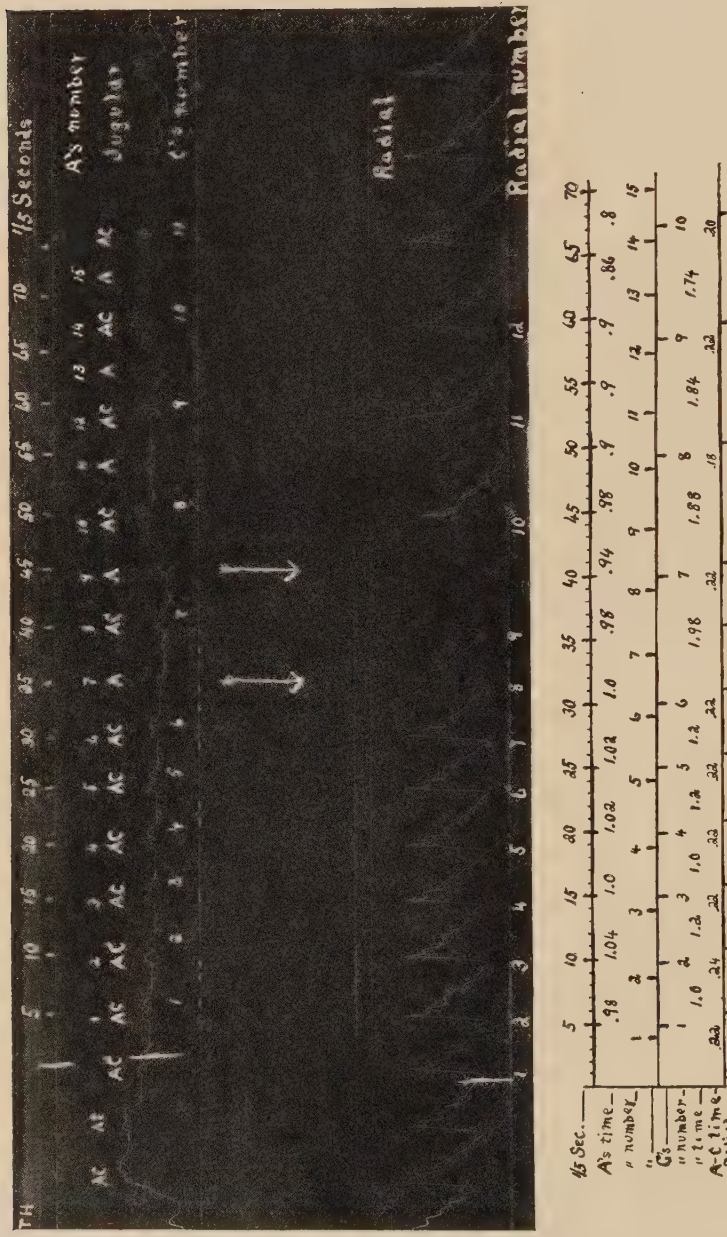

FIG. 5.—February 17, 1910. Change from the normal rhythm to a 2 to 1 rhythm. Note that the seventh *a* wave is *not* followed by a *c* wave, although it *is* accompanied by a wave in the radial (No. 8), and that the ninth *a* wave is *not* followed by a *c* wave and is *not* accompanied by a wave in the radial.

involved or damaged than the division going to the left ventricle, but if further similar findings had been noted, possibly such a localization could have been made.

4. The earliest reference to hemisystole we could find was in an article by Charcelay in 1838, who wrote a memoir on some remarkable cases of asynchronous contraction of the ventricles of the heart. Then in 1868 von Leyden[1] reported the first of his series of cases, the last of which appeared in 1908, forty years later. These cases of von Leyden's have been considered by most other writers as typical examples of pulsus bigeminus. Hering, in particular, has been very insistent upon this point, and thinks that the term hemisystole should be abolished, because although on inspecting the hearts of dying animals one can observe one ventricle beating after the other has ceased to beat, or one ventricle contracting more rapidly than its fellow, such contractions as these can only be noted in dying hearts, and are not, he thinks, compatible with life.

Barker and Hirschfelder,[2] in a very important paper entitled "The Effects of Cutting the Branch of the His Bundle Going to the Left Ventricle," reported that they found, when they cut the left branch without injuring the right, that complete block resulted, but both ventricles contracted synchronously. In one experiment no block resulted, and they, therefore, conclude that the bundle of His plays little if any role in the coördination of the two ventricles.

Eppinger and Rothberger[3] report some studies of the consequences of section of Tawara's branches of the conducting apparatus. Their observations of the electrocardiograms they obtained showed after section of the left branch a curve significant of right-sided extrasystoles, and on section of the right branch, left-sided extrasystoles. When the ventricular contractions are infrequent, the auricular waves can be seen before the ventricular. The authors conclude from their studies that the stimulus originating in the auricles passes down through the bundle of His to its division and then to the left and right ventricles through the branches. When the left branch is cut, the impulse does not flow to the left ventricle, and it is, therefore, not stimulated to direct

[1] Virchow's Archiv, 1868.
[2] Trans. Assoc. Amer. Phys., 1909.
[3] Ztsch. f. klin. Med., lxx, 1.

contraction; the right ventricle contracts first and the left receives its impulse in an indirect way through the right. This state of affairs is the same as occurs when in case of vagus inhibition the right ventricle is stimulated from its wall and consequently contracts before the left. The authors obtained somewhat similar results in a previous study in which cardiac lesions were produced by injections of silver nitrate solution.[1] They refer to the fact that Aschoff had raised the question in connection with his pathological studies whether a lesion of one of the Tawara branches or its division would not impair cardiac action, and Monckeberg has shown that ecchymotic hemorrhage and subendocardial fatty metamorphosis is apt to occur in the position of the conducting bundle and its branches. The authors finally call attention to the fact that in their operations on dogs, section of one Tawara branch was followed by gallop-rhythm characterized by a disturbance of synchronous contraction of the ventricles. In the Medical Clinic of Vienna they recently observed two fatal cases in which during life the form of the electrocardiogram had suggested a diagnosis of interruption of conduction to one ventricle. The autopsies showed macroscopically a large myocarditic lesion in the septum. How far this may have invaded the conducting tissues will have to be determined by careful microscopic examination.

5. Pulsus bigeminus simulates hemisystole because the second or smaller beat, which is an extrasystole, although giving a distinct wave in tracings made from the apex and in the neck does not give any wave in the radial. McKenzie has always insisted that the *c* wave was caused by the carotid, and this view has been adopted by some and rejected by others. It is our belief that the *c* wave can be caused by the carotid artery if the recorder be placed directly over this vessel, but we also believe that by moving the recorder a venous wave can be obtained that has nothing to do with the carotid but comes from the right ventricle. In other positions both these factors undoubtedly may take part in the formation of the so-called *c* wave.

6. A study of a number of the tracings showed that when the rhythm was normal the *a–c* interval averaged 0.2208 second, this

[1] Wien. klin. Woch., 1909, No. 31.

figure being taken from 60 measurements; when the rhythm was 2 to 1 the *a–c* interval averaged 0.205 second, as estimated from 24 measurements; when the rhythm was 3 to 1 the same figure was obtained from the average of 7 measurements. Greater variations were noticed in the length of the *a–c* interval during normal rhythm than at other times. No evidence of progressive increase in the length of the *a–c* interval leading up to a partial block was found at any time.

7. That the auricular rate is slower when normal rhythm exists and faster when a 2 to 1 rhythm has come on is found to be true from a series of measurements taken from a number of tracings. These changes in rate come on immediately after the change one way or other sets in, but we find that there is a greater immediate disturbance of the auricular rate of contraction when the rhythm changes from a 2 to 1 to a normal rhythm than when the normal changes to a 2 to 1 rhythm. Thus, we find an average drop of some 17.9 beats per minute in the rate or a change from 74.2 to 56.3 when there was a restoration to normal rhythm; while when the norma. rhythm changed to a 2 to 1 rhythm there was an increase in the auricular rate of but 10.6 beats in the minute or a change from 59.7 to 70.3. These averages were obtained by measuring only about 20 beats immediately following the change in rhythm.

8. In attempting to determine the cause of greater auricular rate during 2 to 1 or 3 to 1 rhythm than when no dissociation existed, it has occurred to us as reasonable that the interference with auricular outflow, which is present at each alternate or third auricular contraction, would necessarily leave the auricle relatively unemptied, and would thus occasion an earlier stimulus to contraction, which would result in a more rapid rate. When a change from normal to 2 to 1 rhythm occurs the quickening of auricular rate is less prompt than is the slowing when a 2 to 1 rhythm changes to the normal. An explanation for this circumstance may be found in the fact that resumption of normal rhythm after a 2 to 1 rhythm at once relieves the auricle of back pressure and the consequent stimulus to increased rate. Such a sudden relief is followed by prompt re-adjustment of auricular activity, whereas the effect of change from normal to a 2 to 1 rhythm and the consequent gradual overfilling of ventricle and auricle would be met by a slower response.

In this case during the time of complete block the ventricular rhythm was not at all times regular, as has been already mentioned, although the ventricle usually contracted about 20 times to the minute, or about every three seconds; at other times there were irregular pauses, the longest being 5.4 seconds. There were, however, no extrasystoles at any time. It is known from physiological experiment that, owing to poorly developed or retained independent rhythmicity, a portion of the ventricle, as, for example, the severed apex of the ventricle, tends to cease contracting after a time and will resume regular contractions only after an external stimulation. It is, therefore, possible that the continued action of the ventricle sometimes for long periods and despite occasional long pauses in cases of complete block may be due to the stimulus of distention with blood resulting from the continued auricular action.

DISCUSSION.

Dr. A. W. Hewlett: Dr. Stengel's interpretation of his tracings appears to me to be highly probable. The main objections to cardiac hemisystole have come from the experimental side. I have succeeded in cutting one branch of the bundle of His in a perfused dog's heart, but, like Barker and Hirschfelder, I obtained no dissociation of the two ventricles. However, the number of clinical cases which seem to show a dissociation or a lack of synchronism between the two ventricles is such that this may eventually be recognized as a distinct condition.

Dr. Walter B. James: In any explanation of the electrocardiograms of the condition Dr. Stengel has shown, it is not necessary, in order to explain those, to assume a complete dissociation of the right side of the heart in the sense of a complete hemisystole. There is systole of one side of the heart without a systole of the other. It seems to me that by cutting the bundle of His on one side, the impulse will be delayed; there is a delayed transmission to that ventricle. Both ventricles contract, but one contracts by reason of the impulse carried through the bundle of His; the other contracts because of impulses conveyed, though carried through the bundle itself, and this may be a true explanation of the electrocardiograms. There is a complete systole of one side and a slowness on the other.

Dr. W. S. Thayer: I am very much interested in these charts presented by Dr. Stengel, in which there was shown, alternating with the normal rhythm,

an incomplete block, without a delay in the conduction time. As I understand him, every now and then there was an alternating beat which dropped out without delay in A-C time. It is an interesting question whether or not this should be called a condition of heart block. I have seen several such cases in the past two years. One individual, without any delay in his A-C time, showed a dropping of alternating beats after exercise or after any emotion. In a similar instance, without any delay in the A-C time, atropine cleared up several attacks immediately. I should like to ask Dr. Stengel if he might not explain such tracings as being dependent upon a lack of contractility or irritability of the ventricle, or whether, perhaps, one might not fancy that the intensity of the stimulus was diminished without delay in the conduction time?

Dr. Alfred Stengel: There is but one point which I wish to refer to in answer to previous discussion, and that is as to the existence of a true heart block in this case. An inspection of the tracings when there was a complete block will show that there was complete dissociation. At times when there was not complete block, we did not detect any progressive lengthening of the transmission time from the stay of regular action to that in which a partial block was established.

AN EXPERIMENTAL STUDY OF THE RESISTANCE TO COMPRESSION OF THE ARTERIAL WALL.

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I. Object.

The object of this study was to determine whether the resistance to compression of the arterial wall introduces an error of any importance in the clinical measurement of systolic blood pressure by methods employing circular compression of the arm.

II. Previous Studies and Present Status of the Question.

Very few studies of this problem have been made, and none of these can stand criticism. Von Basch[1] measured crudely the pressure necessary to close the empty radial artery. He found this required 1 mm. for normal, and not much above 5 mm. for sclerotic vessels.

Martin,[2] in a few experiments on the normal carotids of man, horse, and dog, found that a pressure of 2 mm. was sufficient to collapse the arterial wall; in arteries from an advanced case of arteriosclerosis only 7 mm. were required.

No subsequent direct experiments were made until 1908 by

[1] Der Sphygmomanometer und seine Verwerthung in der Praxis, Berl. klin. Wochenschr., 1887, xxiv, 181.

[2] The Determination of Arterial Blood Pressure in Clinical Practice, Brit. Med. Jour., 1905, i, 865.

Herringham and Womack,[1] who examined carotid, iliac, and brachial arteries from 49 bodies, removed post mortem. The results were very startling, showing wide variations in the compressibility of these vessels, the extremes in the case of the brachials being from 4 to 34 mm. These variations could not be brought into relation with the age of the individual, the condition of the arterial wall, its expansibility under high internal pressure, nor the disease causing death. Furthermore, marked differences were found between carotid, iliac, and brachial from the same individual, and the two brachials differed by as much as 10 mm.

The obvious criticism of these results, as casting a doubt on human blood pressure measurements, is that they were done on dead arteries, and this was promptly made by Hill,[2] who also objected that, for proper comparison, blockage of the pulse wave and not cessation of the flow should be the criterion,

Herringham,[3] subsequently, in a discussion of the subject, cited a few further experiments performed on arteries killed by soaking in sodium fluoride solution, still showing an appreciable resistance to compression, the highest being 22 mm., and an especially high figure from a patient who had had hypertension during life. He considered that these experiments were a sufficient reply to Hill's objection.

Since the completion of our work two new papers have appeared, reporting observations of a different kind. Scholtyssek[4] performed a few experiments similar to Herringham and Womack's, using arteries from the dog, rabbit, and horse, and two human vessels. In all cases the arteries were compressed at less than 3 mm. Hg, except one digital artery from the horse, which required 24 mm. The circulating medium seems to have been water; temperature was disregarded, and a very low internal pressure appears to have been used. He also tested the resistance of a living carotid from a rabbit. Attaching it to one carotid of another animal, thus maintaining in it a normal blood circulation, the pressure necessary to obliterate the flow from it was determined, while direct manometric

[1] Proc. Roy. Soc. Med., 1908, ii, 37, Med. Sect.
[2] The Measurement of Systolic Blood Pressure in Man, Heart, 1909, i, 73.
[3] Proc. Roy. Soc. Med., 1909, ii, 238, Med. Sect.
[4] Arch f. Anat. u. Physiol., 1909, Physiol. Abt., 323

readings were made from the opposite carotid. His results he considered showed a resistance of 2 mm. Hg for the rabbit's carotid; of 7, 8, 15, and 11 mm. Hg for a dog's similarly tested. The most obvious criticism of these figures is, that there was not absolute synchronism between his readings of compressibility and the rapidly fluctuating blood pressure of the animal, since the former were not recorded graphically. The results, however, have real relative value, though the vessels of such small animals are scarcely comparable with the human brachial.

Schmidt [1] describes a number of observations on freshly removed dog and rabbit arteries by a similar method. He tested, in rather unsystematic fashion, the effect of varying internal pressure, of temperature, of painting with adrenalin and with chloral hydrate, of death of the vessels. Normal saline or blood was his circulating medium. He concludes that the resistance varies with the vessel and with the time after removal, no more change in resistance occurring after twenty-four hours. With increase of the internal pressure, the resistance may increase, diminish, or remain constant. With large arteries from these animals he found the resistance to range between 1.84 and 7.38 mm. Hg. He was unable to produce noticeable constriction by painting on adrenalin, or dilatation by chloral hydrate. He did obtain changes associated with temperature; the higher the temperature the lower the resistance to compression.

This work is open to many of the objections urged against the preceeding. In addition, segments of artery only 3.5 to 4 cm. long were used. This is of less importance than with thicker vessels, though not negligible. Schmidt evidently dealt with live arteries, and his work is of interest on that account, but conditions were not accurately controlled. As with Scholtyssek's experiments, the results do little to solve the problem of the resistance to compression of the human brachial artery.

Others have approached the problem by altogether indirect methods, or, accepting v. Basch's figures, have considered the arterial wall a negligible factor in clinical blood pressure measurement. To the latter opinion, one of us [2] has formerly held.

[1] Arch. f. Anat. u. Physiol., 1909, Physiol. Abt., 331

[2] T. C. Janeway, The Clinical Study of Blood Pressure; D. Appleton & Co., New York and London, 1904, 60.

Williamson,[1] has made a study of the question by comparison of the systolic pressures in the arm and leg. He claims to have found very marked differences in high pressure cases, which he interprets as due altogether to the vessel wall factor, assuming that the thickness of the wall of the leg arteries and extensive arteriosclerosis in them is quite regularly greater than in the brachial artery.

Hill, in his discussion of the paper and his subesquent publication, takes direct issue with Williamson on the accuracy of his observations, and has shown how slight tension in the leg muscles, or lack of simultaneous measurement of the pressure, may lead to serious error in the result. Hill's own investigation of the blood pressure in the arm and leg failed to show any appreciable difference in the readings, except in the case of free aortic regurgitation, if certain precautions were taken. Hill has also shown that the superficial venous pressure may be raised to within 10 mm. of the obliterating pressure in the brachial as measured by the armlet, and has made measurements from two arteries at different levels, which differed by exactly the hydrostatic pressure of the blood column which separated them. Hill concludes that we have no evidence that the resistance of the arterial wall to compression affects the systolic index of blood pressure, but that the relative softness or hardness of the arterial wall affects the conduction of the systolic wave and so modifies the readings. These readings, however, would in his opinion correspond to real differences in the systolic pressure within the arteries.

Oliver,[2] also approaching the question by an indirect method, comparison of the measurement by an armlet with the measurement by his hemodynamometer, considers that he has demonstrated very large errors in the systolic pressure measured by the armlet method; that human arterial pressure, even in disease, seldom exceeds 200 mm. and never rises above 250 mm., all higher readings being due to factors inherent in the vessel wall.

Von Recklinghausen[3] has shown how sclerotic vessels may be

[1] Proc. Roy. Soc. Med., 1909, ii, 229, Med. Sect.

[2] Studies in Blood Pressure, second edition, London, 1908, 111.

[3] Ueber Blutdruckmessung beim Menschen, Arch. f. Exper. Pathol. u. Pharmakol. 1901, xlvi, 78.

obliterated at the centre but stand open at the corners, as an explanation of the mechanical difficulties in the way of easy compression of thick-walled vessels.

On the other hand, such observations as that of Hensen,[1] of extremely low systolic readings in a sclerotic brachial artery, and similar ones which all who use the sphygmomanometer extensively have encountered, have seemed to make any marked influence of the sclerotic vessel wall very questionable.

Finally, Russell,[2] in his recent book, takes the ground, altogether from a priori considerations, that the state of tonus of the vessel wall is probably even more important than the actual blood pressure in producing the high readings obtained by our clinical instruments. Hypertonus of the vessel wall, rather than arterial hypertension, is what he believes is measured. Russell adduces no experimental evidence, except from an artificial scheme with rubber tubing, but takes the stand that such high blood pressure readings as are clinically recorded are inconceivable; that most of the variations in these readings, occurring spontaneously or produced by drugs, are due to change in the tonus of the vessel examined; and, though conceding the value of the sphygmomanometer for measuring these variations in vessel tonus, insists that the estimation of the caliber and degree of contraction of the radial artery by the educated finger is still more important. Russell does not explain clearly how such extreme hypertonic contraction of the vessels can fail to be associated with marked increase in the peripheral resistance and therefore of the blood pressure. One gains the impression from his book that extreme hypertonus of such large arteries as the brachial or radial occurs independently of constriction of the arterioles. He also goes so far as to state that rubber tubing is a more accurate counterpart of the living artery than is a dead artery removed post mortem.

The only other work bearing in any way on the problem at issue has been a comparison of the indirect manometric blood pressure record, made during the course of an amputation, with simultaneous

[1] Beitr. z. Physiologie und Pathologie des Blutdrucks, Deutsch. Arch. f. klin., Med., 1900, lxvii, 443.

[2] Arterial Hypertonus, Sclerosis, and Blood Pressure, Phila., 1908, J. B. Lippincott Co., 87.

indirect readings made on the other arm or leg. Such observations have been published by Müller and Blauel,[1] and more recently by Volhard.[2] With the v. Recklinghaushn apparatus and 12 cm. armlet, the former found that it required a pressure of 7 to 10 mm. above the true systolic pressure within the artery to obliterate the pulse wave. With the Gärtner method, or still more with the old Riva-Rocci apparatus and its narrow armpiece, this error became greatly exaggerated. The patients all had approximately normal vessels. Volhard reports a slightly greater difference, 13 mm., in a patient with normal blood pressure; as much as 20 mm. in one with hypertension. He only alluded to his results somewhat briefly. Since one of us[3] has shown that the soft tissues of the arm are practically negligible as a source of error, these results speak strongly for some influence of the artery wall.

These altogether conflicting views and the disagreement in the results obtained by indirect methods of approaching the problem pointed so clearly to the need for accurate experimental data, obtained under conditions which should be beyond criticism, that we were impelled to undertake the study of the question by methods subsequently described.

III. Plan of the Experiments.

The plan originally in mind was to study the compressibility of adult human arteries obtained post mortem, and of infants' arteries, with a view to determining the influence of thickness of wall, atheroma, and calcification; and to attempt to obtain surviving human arteries from amputated limbs. It was hoped that from these not only might an accurate idea of the compressibility of live arteries be obtained, but that the influence of tonus might also be tested, by introducing adrenalin into the circulation through the vessel. Such arteries, however, proved very difficult to procure, and had many

[1] Zur Kritik des Riva-Roccischen und Gärtnerschen Sphygmomanometers, Deutsch. Arch. f. klin. Med., 1907, cvi, 517.

[2] Ueber die Messung des diastolischen Blutdruckes beim Menschen, Verhandl. D. Kong. f. inn. Med., 1909, xxvi, 200.

[3] T. C. Janeway. The Influence of the Soft Tissues of the Arm on Clinical Blood Pressure Determinations, Arch. Int. Med., 1909, iii, 474.

small branches requiring ligature. The experiments were rather unsatisfactory, because of the doubt as to the life of the vessel, when finally prepared; and their number was insufficient to give conclusive results.

Since Meyer[1] has shown that the carotid of the ox, kept in ice-cold Ringer's solution, preserves for days its capacity for responding to electrical stimulation, adrenalin and other vasoconstrictors, ox carotids, brought from the slaughter house in cold Ringer's solution, were used for the study of the effects of tonus, and later a few experiments were done on mesenteric arteries from the ox.

Meyer found extreme contraction in ox carotids removed in this way, which in his experiments required stretching with heavy loads to overcome, and MacWilliam and Mackie,[2] have noted a similar persistence of contraction in certain postmortem arteries and arteries removed at amputation. It seemed to us, as to them, that herein might lie the chief explanation of Herringham and Womack's[3] discrepant results. Therefore we believed that measurements made on such surviving animal arteries, under varying absolutely known conditions, would give information of far more value for the elucidation of the physiological question at issue than the study of many dead arteries.

Finally the plan included a study of the compressibility at different internal pressures, of the influence of the length of the segment of vessel examined, of other sources of experimental error, and the testing of some elastic and non-elastic tubes other than arteries.

IV. Material Examined.

The material examined was as follows:

1. Twelve common carotids from infants, removed post mortem, of which ten gave results free from obvious error.

2. Twenty-three common carotids and four iliacs taken from adults, removed post mortem, of which twenty gave results free from obvious error.

[1] Ueber einige Eigenschaften der Gefässmuskulatur mit besondere Berücksichtigung der Adrenalinwirking, Ztsch. f. Biol., 1906, xlviii, 352.

[2] Observations on Arteries, Normal and Pathological, Brit. Med. Jour., 1908, ii, 1477.

[3] Loc cit.

3. Six arteries taken from amputated limbs, of which four gave results free from obvious error.

4. Thirty-eight common carotids and four mesenteries from the ox, of which eleven gave results free from obvious experimental error.

5. Six samples of rubber tubing of different caliber and lumen; one boiled artery; one œsophagus; one segment of small intestine.

V. Method.

1. *Apparatus.* The artery *AA* to be examined, after careful ligature of its branches a short distance from their emergence, was tied securely over the ends of two glass cannulæ *BB′*. Except in the case of the infant's arteries, these cannulæ were cut off squarely; for the smallest infant's vessels bevelled cannulæ had to be used, but these we believe may be a source of error, a small portion of the artery being collapsed over the opening of the cannula before its lumen elsewhere has been obliterated. The artery was then placed in a glass cylinder *C*, of 21 cm. length and 2.5 cm. diameter, with a capacity of 52.5 c.c. after insertion of the stoppers, as shown in Fig. 1. The cannulæ *BB′* project through rubber stoppers *DD′*, at either end. For convenience in the insertion and removal of the vessel, one of these stoppers *D′* was split through one-half its diameter. The other stopper *D* was pierced by a second opening for the insertion of the thermometer E^1. The cylinder carried near one end two glass tubes, *F*, *G*, set in opposite points on its circumference and communicating with its lumen. The lower of these tubes (*F*) was connected by rubber tubing with a pressure bulb, which was suspended from the ceiling by a pulley and rope and could be raised and lowered at will, and which will be called the external circulation, and through a T-tube with a recording mercury manometer which at all times registered the pressure in the external circulation and the cylinder. The upper tube (*E*) was for the escape of air from the cylinder in filling, after which it was closed by a rubber tube and a pinch cock. The cannula (*B*) was similarly connected with a pressure bulb which could be raised

or lowered at will, which will be spoken of as the internal circulation and by a T-tube with a recording mercury manometer. The other cannula (B') was connected by rubber tubing with a T-tube (H), the stem of which was connected by pressure tubing with a Hürthle membrane manometer. The opposite end of the T-tube was connected by rubber tubing with a capillary armed with a stopcock. The manometers connected with the external and internal circulations, and the Hürthle manometer, which registered the pressure changes in the outflow from the artery, were made to write upon a kymograph, and all the steps in the experiments were graphically recorded. For convenience, the manometer attached to the internal circulation was made to write a little distance (about 10 mm.) above

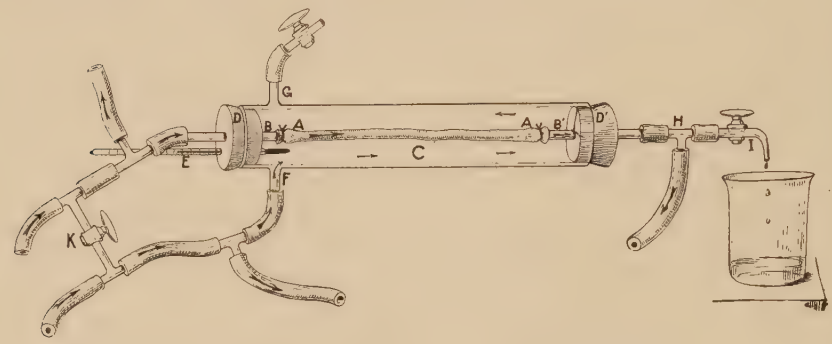

Fig. 1.—Diagram of apparatus.

that of the external circulation, and just enough behind it so that the writing points did not touch when at the same height. The Hürthle manometer record was carried at the bottom of the drum. In order to obviate the complication of two zero lines, where only differences in pressure were to be measured, the two circulations were connected by the branch (K), closed by a stopcock. Before and after each reading, this stopcock was opened and the pressure in the two circulations allowed to equalize. The relative positions of the two manometers were then recorded. These lines of equal pressure were used for all subsequent measurements, and the approximate accurate pressure as measured by the scale on the manometer was written on the tracing, if this was varied during the course of an experiment.

For the experiments on live arteries two other pressure bulbs were employed, connected with the internal circulation just before its attachment to the cannula *B* by means of a Y-tube. All the rubber tubing used was of the heaviest pressure tubing of 3 mm. bore. The cylinder containing the artery was itself encased in a large water jacket, which has been omitted from the diagram for the sake of simplicity. The internal circulation was also carried through large water jackets in spiral glass tubes. The various water jackets were connected with one another and a uniform circulation maintained through them by means of which both the internal and external circulations were always kept at the same temperature, which could be varied between that of tap water, about 15° C., and 37° C.

2. *Technique for Postmortem Arteries.* The technique of the measurement of the compressibility in any postmortem vessel was as follows: The artery was placed in the cylinder with great care to avoid any twisting on its axis or undue longitudinal stretching. The flow was then established through it from the internal circulation until all the air had been driven out through the capillary and Hürthle manometer. The external circulation was then connected with the cylinder until the latter was filled and the last bubble of air driven out through the tube *G*. The circulations were then connected through the branch *K* and the manometer heights and the position of the Hürthle manometer recorded. The drums were then stopped and the branch *K* closed. The bulb of the external circulation was then slowly raised until the level of the Hürthle manometer began to fall, when the drum was again started and this pressure, marking the beginning of collapse of the artery, recorded. This corresponded, as a rule, to a marked diminution in the outflow from the capillary. The drum was again stopped and the pressure in the external circulation gradually raised until no drops whatever came from the capillary. The Hürthle manometer was then at zero, and another record of this point, the point of complete obliteration of the artery, was made. The stopcock in the capillary was then closed and the pressure in the external circulation gradually lowered until the level of the Hürthle manometer began to rise. A record of this point was also made. Fre-

quently a single drop would get through the vessel without the flow being reëstablished, apparently due to a little unevenness in the lowering of the pressure, so that waves were produced. If so, the lowering was continued until the Hürthle manometer showed a visible continued rise. This corresponded to an outflow from the capillary of about one drop every three seconds. This point was considered the pressure at which flow through the artery was resumed. After this the bulb was lowered to the original point, the stopcock on the branch *K* was re-opened, and another reading recorded after the pressure had equalized. In the case of postmortem vessels, such readings were made with internal pressures of 30 mm., 100 mm., and 150 mm. Hg. In these experiments the temperature was not controlled.

Ringer's solution was used for both the internal and external circulation in all the experiments, except where it was desired to test the effect of other substances.

3. *Technique for Surviving Arteries.* In the experiments on living vessels the technique was somewhat different and was a matter of great importance. Only after a number of experiments were our results free from various sources of error described below. The arteries were roughly removed from the animal with the surrounding fascia and fat and put at once in a large jar of ice-cold Ringer's solution, in which they were brought to the laboratory. The artery was then dissected free from the sheath, with as little removal from the solution as possible, and the branches ligatured as found, care being taken that the ligatures were placed a short distance from the origin of a branch, in order to avoid any deformation of the artery itself.

A portion of the artery not less than 7 cm. long was then cut off and the cannula inserted into its ends and securely tied. The vessel and cannula were then left in cold Ringer's solution until a segment of the remainder of the vessel 8 mm. long had been cut off. The ring thus obtained was cut across, making a strip, which was securely ligatured at each end, the ligature being tied into a loop for suspension in the muscle chamber as described by Meyer.[1]

[1] Loc cit.

This strip of artery will be referred to hereafter as the Meyer strip. The cannula *B* was then inserted into the stopper *D*, the Meyer strip having also been placed in the cylinder, and by placing the stopper *D′* on the cannula *B′*, before inserting it firmly into the cylinder, the apparatus was held vertical for a moment and the artery allowed to assume a natural position, suspended as it was from its upper end. In this way all twisting of the artery around its long axis was obviated. The stopper *D′* was then inserted tightly, the cylinder put in place and filled with cold Ringer's solution from the external circulation. The internal circulation was then connected with the cannula *B*, and the Hürthle manometer and outflow capillary with the cannula *B′*, and Ringer's solution allowed to flow through the artery until all the air could be driven out, great care being taken that the internal circulation should never be above the pressure of the external circulation, in order that there should not be the least stretching of the vessel during this part of the procedure. Then the coldest possible temperature being maintained in the water jacket, a measurement of the compressibility of the tightly constricted cold artery was made. This reading and all others were made exactly as described under post-mortem arteries, the three points, of beginning of collapse of the artery, of total cessation of the flow, and of the first resumption of the flow as shown by the Hürthle manometer, all being recorded. Such vessels, during this part of the procedure, were of exceedingly small lumen, with rigid walls, and offered marked resistance even to bending. These readings were made with an internal pressure of 70 mm., the obliterating pressure being so great that we were unable to obtain the necessary difference in levels between the bulbs with the internal circulation set at any higher point. After one or two readings made with cold vessels, the temperature in the whole apparatus was raised to 37° C. by warming the reservoir feeding the water jacket, and maintained as nearly as possible throughout the rest of the experiment. As soon as the temperature had reached 37° a second measurement of the obliterating pressure was made.

At this point the circulations were shut off and the Meyer strip removed from the cylinder, which was then closed. Then the circulation was re-opened and the outflow through the capillary

closed. The pressure in the internal circulation was then raised to 100 mm. and that in the external lowered to zero, and the pinch cock on the tube *G* opened. This subjected the artery to an internal distending pressure of 100 mm. and caused a very great increase in its diameter. At the same time, observation of the escape of fluid from the open end of the tube *G* served to detect any unrecognized leaks, which would vitiate the experiment. The Meyer strip was transferred at once to the muscle chamber containing Ringer's solution, kept at 37° C. by a water bath, and connected with a light muscle lever magnifying six times, following the exact technique laid down by Meyer. This strip was then stretched with a load of 90 grams for carotids, 70 grams for mesenteries, during the period of stretching of the artery in the cylinder, these loads having been found by Meyer to be sufficient to completely overcome the contracture of the vessel in fifteen minutes. After a lapse of not less than fifteen minutes the pressures in the internal and external circulations were again brought to 70 mm. and a measurement of the compressibility of the now completely relaxed artery was made. Following this, the load on the Meyer strip was reduced to 50 grams for carotids and 20 grams for mesenteries, and sufficient time given to allow the artery to become adjusted to this load, as shown by the muscle lever writing a horizontal line.

The next step was the substitution for the internal circulation of Ringer's solution of a solution of adrenalin chloride in Ringer's solution, 1 in 100,000 or 1 in 50,000. When this had flowed through the artery for one minute, another measurement of the compressibility was made with as much expedition as possible. On its completion the Meyer strip was similarly tested, Ringer's solution in the chamber being replaced by adrenalin in Ringer's solution of strength equal to that used in the artery, and the contraction of the strip recorded on a drum. Finally, an internal circulation of barium chloride in Ringer's solution, 2.5 to 5 per cent., in different experiments, was substituted for the internal circulation and allowed to flow through the artery for three minutes, after it could be identified in the outflow by its precipitation by sulphuric acid. This considerable time was given because of our observation of the long latent period before contraction to barium chloride in

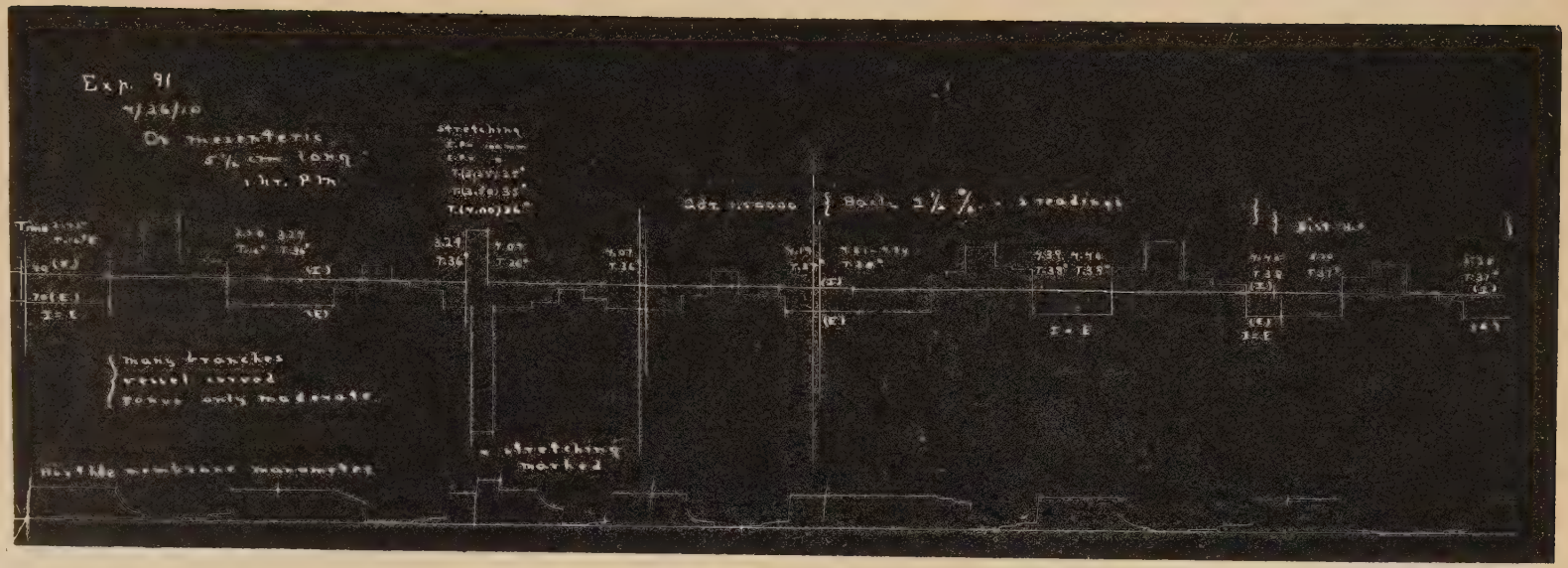

FIG. 2.– Typical tracing from a surviving artery. Upper line (*I*). Record of manometer connected with internal circulation through artery. Pressure, 70 mm. Hg. Second line (*E*). Record of manometer connected with external compressing circuit. Third line. Tracing from Hürthle membrane manometer connected with outflow from artery. Base line. Base line of Hürthle manometer.

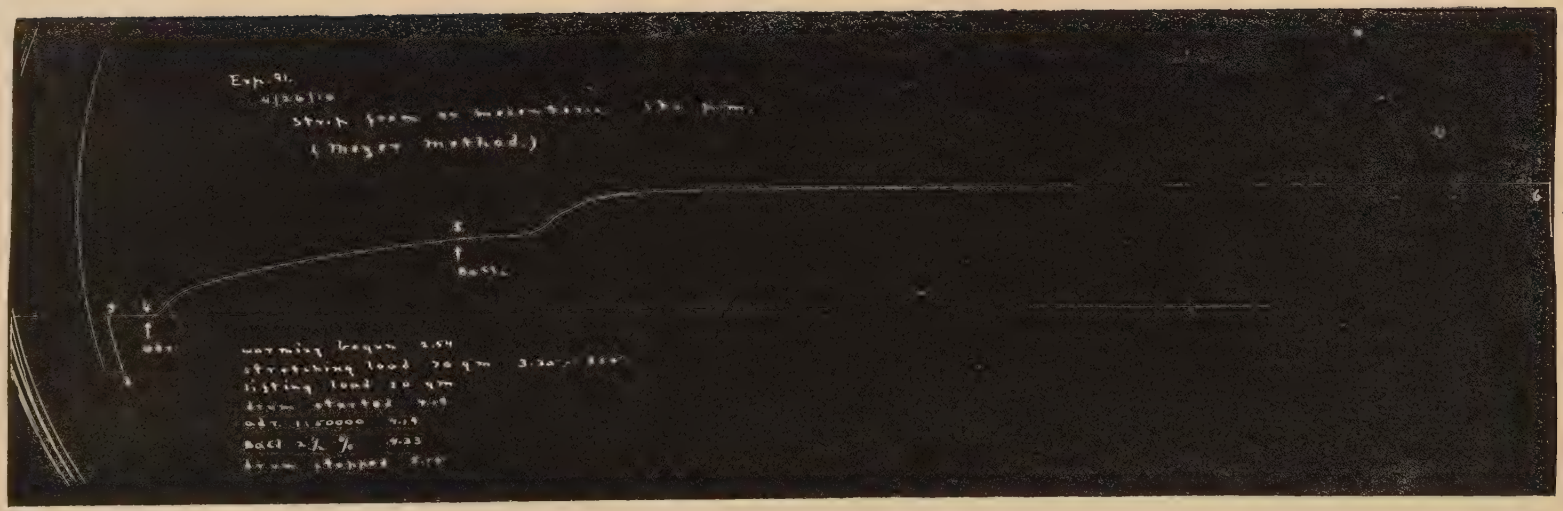

FIG. 3.- Tracing of Meyer strip control from artery of Fig. 2. 1. Large fall of muscle lever during stretching with 70 grams. 2. Rise of lever on reduction of load to 20 grams. 3. Horizontal trace, showing equilibrium of strip. 4. Rapid contraction from adrenalin, 1 to 50,000. 5. Additional rise from barium chloride, 2.5 per cent. solution. (Note latent period and persistence of contraction for forty-two minutes.) 6. Gradual fall of lever during succeeding twenty-four hours, showing slow return of artery toward original length.

the Meyer strip. At the end of three minutes the compressibility of the artery was again measured, and in certain cases two or three successive measurements were made. On the completion of the first, the reaction of the Meyer strip to barium chloride was tested in the same way as to adrenalin.

By the technique described we obtained tracings such as are reproduced in Fig. 2 and Fig. 3.

By measuring the increment of external pressure used to produce collapse of the artery, complete cessation of flow, and the first resumption of the flow after obliteration of the lumen of the artery, we believe we have obtained a clearer conception of the mode of compression of the vessel and have obtained results more comparable with criteria used in clinical blood pressure determinations than have previous observers. In addition, we have determined for living ox arteries the effect upon their compressibility of extreme contracture produced by cold, as compared with the compressibility of the same vessel when warmed and when subsequently warmed and stretched to complete relaxation; and of vasoconstriction produced by adrenalin and by barium chloride; the surviving character of the vessel in all cases having been proved by the subsequent reaction to similar adrenalin and barium chloride solutions of a Meyer strip from the same artery, subjected throughout to identical conditions.

The technique in the case of some of the amputation vessels was the same as for the living ox arteries, but in no case have we been able to obtain a definite reaction in the Meyer strip, and we are therefore unable to predicate the surviving character of any of these human arteries. They must, therefore, be considered as representing unusually fresh dead vessels.

The most difficult problem connected with these arteries of the extremities is the ligaturing of their very numerous branches and the consequent excessive handling and waste of time. We do not despair, however, of being able so far to perfect our procedure as to obtain results similar to those had with the animal vessels.

VI. Sources of Experimental Error.

The various sources of error through which it became necessary to discard large numbers of experiments were as follows:

1. *Air Locks.* The locking of the internal circulation by a bubble of air at the mouth of the outflow cannula, or at some turn in the tubing, was a troublesome source of results which had to be discarded in our earlier experiments, but which we carefully guarded against later.

2. *Leaks in the Vessels.* Even after careful ligature of all visible branches leakage occasionally occurred. This was due either to a minute branch concealed beneath the outer connective tissue coat, or to small holes where branches had been pulled out and the adventitia slipped over the opening, concealing their existence; or to slipping of ligatures. The method of testing already described showed the most minute leaks, and some such test is absolutely necessary. In the case of a minute branch, allowing a very slight escape of fluid outward at an internal pressure of 100 mm. Hg, we did consider that there could be flow in the reverse direction at a difference in pressure of only 10 or 20 mm. Hg. With all other forms of leak the experiment was discarded.

3. *Torsion of the Vessel.* Any twisting of the vessel around its long axis is liable to introduce a very large error, though this is not constant. We are convinced that any experiment in which this possibility was not recognized and carefully guarded against cannot be accepted at all. We are inclined to believe that some of Herringham and Womack's[1] unintelligible results may have been due to this cause.

4. *Longitudianl Torsion.* The degree of longitudinal stretching of the artery exerted much less influence on its compressibility than did torsion, but was capable of somewhat increasing its resistance to compression. Undue stretching was therefore carefully avoided.

5. *Insufficient Length.* The length of the portion of artery examined proved a marked factor in determining its resistance to compression, as might be expected from v. Recklinghausen's[2]

[1] Loc. cit.

[2] Loc. cit.

demonstration of the error introduced by the narrow arm piece in clinical blood pressure measurements. This influence, like that of torsion, was exceedingly variable. The following experiments, in which successive tests of different lengths of the same arteries were made, showed clearly the possibility of error from this source.

TABLE I.—Influence of Length of Segment on Compressibility. Adults' Common Carotids, Forty-eight Hours Post Mortem.

Difference of pressure at which flow returned, internal pressure being 100 mm. Hg.

	Before shortening.		After shortening.	
No.	Length in cm.	Pressure in mm. Hg.	Length in cm.	Pressure in mm. Hg.
35	7.5	4	4	39
37	13	13	2	86
38	11	5	3.5	7
42	8	6	3	7
45	12	0.5	4	1
49	9	5	2.5	18

The inconstant occurrence of erroneou sresults from this, and from the previous cause, we are inclined to attribute to variations in the condition of adjacent portions of the wall in many vessels. Presumably the softest bit of wall in the length of artery examined determines the cessation of flow, rather than a uniform compression of the entire vessel; therefore, a short piece of artery, if it contain a thin spot, will be as compressible as a longer one; whereas, if the thin portion happens to be cut off, the resistance to compression will be markedly altered. It seems to us probable, from observation of the mode of collapse of many arteries, that most, if not all, human vessels, are of irregular thickness and compressibility, the weakest spot determining the resistance of the whole; and that long portions give the lowest readings because more likely to contain a thin area.

In addition, there must be some resistance in the very short strips due to longitudinal strain on the indented wall, as described by v. Recklinghausen.[1]

We feel convinced that experiments made upon arteries of less length than 5 cm. clear between the ends of the cannulæ, except

[1] Loc cit.

in the case of very small and thin-walled vessels, are altogether valueless, unless so low a reading is obtained that it can obviously contain no marked factor of error. Since Herringham and Womack[1] described arteries examined by them as being from 2 to 3 inches, that is, 5 to 7.5 cm. long, and since one can scarcely tie the end of the vessel over a cannula without using nearly 1 cm. of it, it seems to us probable that many of their experiments were performed on vessels much less than 5 cm. in length between the cannulæ. We are strongly inclined to attribute many of their discrepant results to this cause, though the state of contraction of the vessels examined by them may have played considerable part.

6. *Differences in Temperature and in Composition of the Artificial Circulation.* In the experiments on living vessels differences of more than a degree or two in temperature either way caused us to reject the experiment completely, and we believe, as a result of a few observations, that a uniform composition of the circulating media is important. For this reason we take exception to the recently published experiments of Scholtyssek[2] and of Schmidt[3] as we have already noted.

Of great interest to us was the corroboration we obtained of Meyer's[4] statement that his vessel strips were exquisitely sensitive to traces of adrenalin, so that pipettes could not be used twice the same day. We were obliged, after losing a number of observations, to allow two days to elapse between experiments, for washing out the last traces of adrenalin and barium chloride from our apparatus.

VII. Tabulation of Results.

The following tables show the results obtained in all our successful experiments on arteries. No experiments have been included in which there was the least suspicion of technical error. For simplicity, and because we do not feel as yet in a position to discuss its significance, the manometer readings for the point of first collapse of the artery have been omitted. For the infant's carotids, complete obliteration of the artery with cessation of flow occurred with such

[1] Loc. cit. [2] Loc. cit. [3] Loc. cit. [4] Loc. cit.

a small increase of external pressure that no measure of the return of flow after compression was possible. In all other tables the pressure at which the flow was completely abolished, and at which it was first reëstablished, as shown by the rise of the Hürthle manometer, are both recorded. In all postmortem vessels, measurements are tabulated at three different internal pressures. The experiments on amputation vessels were carried on at an internal pressure of 100 mm., those on surviving ox vessels at an internal pressure of 70 mm.

For these vessels we have tabulated only the pressure at which the flow was reëstablished through the artery. Throughout all our experiments we have found this point, which is represented by the first steady rise of the lever of the Hürthle manometer, much more constant in its behavior than the point of complete cessation of flow. The reasons for this are somewhat complex and probably dependent upon the exact mode of closure of the artery and the shape of the cross-section of its lumen when compressed. In many cases, after practical collapse of the artery, the flow of a drop every five seconds to even once a minute would persist after raising the external pressure many millimeters. Studies in progress at present upon this point we hope to present later. The amount of flow represented by the first rise of the Hürthle manometer was pretty regularly one drop in three or four seconds from the capillary. We are convinced that this is by far the most constant index of the compressibility of arteries. It is also without question the most analogous to the usual criterion in clinical blood pressure measurements, the return of the pulse after obliteration. We have made a number of observations to determine the relation which this point bears to the passage of a wave through the artery, in order to satisfy Hill's[1] objection to Herringham's[2] results. Our observations upon this point show that the question of the passage of a wave under the mechanical conditions of our experiment is also a complicated one. If the outer compressing medium be in continuity with its pressure bulb and manometer, waves are transmitted from the artery to the compressing solution, which apparently

[1] Loc. cit.

[2] Loc. cit.

may either produce summation or interference with waves within the artery, thus either facilitating or hindering their passage. By clamping off the connection with the pressure bulb this element could be obviated. Under these conditions, waves with the maximum pressure that of the previous internal pressure used in the experiment did not come through at a pressure above that of the

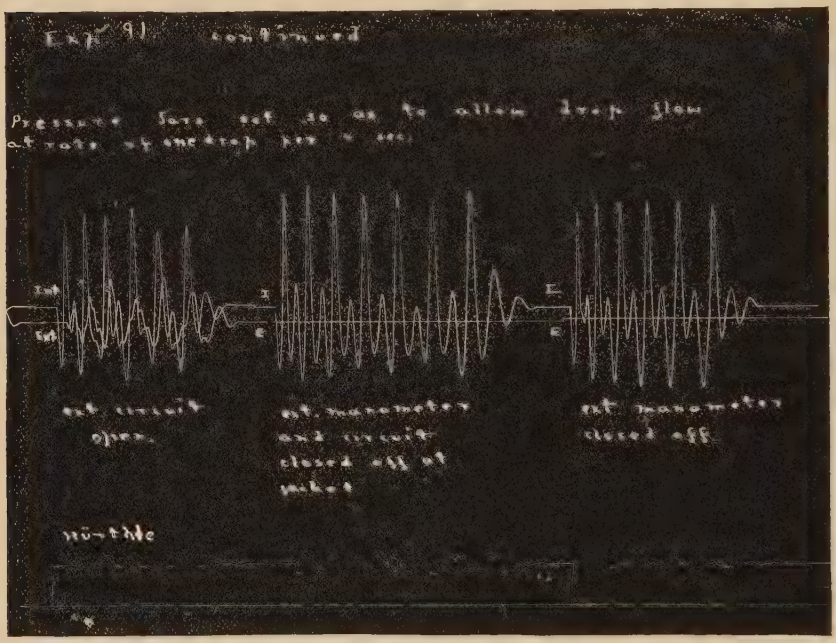

FIG. 4.—Tracing from the same experiment as Fig. 2, showing a wave passing through the artery at pressure of return of flow. Both pressures as at end of Fig. 2. Note different form of wave with external circuit open, allowing waves to be set up in it; with external circuit shut off at the cylinder, and last with the manometer, but not the pressure bulb, shut off.

return of the flow. At this point a slight wave was transmitted. While it would be impossible to investigate all the conditions surrounding the passage of a wave, we feel that the index which we have used, the pressure at which the flow is first reëstablished after compression of the vessel, can be accepted as the closest approximation to the clinical criterion of the return of the pulse wave after obliteration. Fig. 4 shows the difierent forms of wave passing

through the artery, with different conditions for participation in the wave motion by the external circulation.

TABLE II.—Ten Infants' Carotids.

No.	Length in cm.	Time post mortem in hours.	Difference of pressure in mm. Hg at which flow ceased. Internal pressure. 30 mm.	100 mm.	150 mm.
1	7	10	1	1	3
2	6	8	1	3	4
3	4	28	2	3	3
7	5	18	2	3	6
10	5	3	3	5	5
11	6	6	6	6	7
12a	4.5	59	1	3	5
13a	6	6	2	4	5
14	4.5	6	5	8	8
24	6	1	4	4	
Average			2.7	4	5.1

Summary of results of all experiments.
Maximum difference, 8 mm.
Average difference, 3.9 mm.
Minimum difference, 1 mm.

TABLE III.—Twenty Adults' Carotids. All examined more than forty-eight hours post mortem.

No.	Group.	Length.	Difference of pressure in mm. Hg at which flow: Ceased.	Returned.	Ceased.	Returned.	Ceased.	Returned.
22	B	9	8	6	10	3	6	2
23	B	9	12	5	..	..	10	3
29	A	9	30	14	28	16	24	16
30	A	7	26	18	22	19	23	19
31	A	8	18	12	24	14	18	9
32	A	11	18	10	16	11	16	8
33	A	8	22	12	20	12	20	11
34	A	11	13	6	14	8	16	9
35	A	7	17	13	16	8	19	14
36	A	11	14	6	16	6	12	7
37	A	13	14	12	20	13	11	12
38	B	11	10	6	13	5	11	9
39	A	8	9	2	10	1	8	0
41	A	8	16	10	12	8	10	7
42	A	13	13	6	11	6	12	6
45	A	12	3	0.1	3	1	6	2
46	A	11	..	..	11	6		
47	C	4	28	10	25	14	20	10
48	A	7	19	11	15	9	15	6
49	A	9	16	6	8	5	12	4
			16.1	8.7	15.5	8.7	14.1	7.6
Internal pressure			30 mm.		100 mm.		150 mm.	

Summary of Results.

Group.	No. of arteries.	Condition.	Difference of pressure at which flow Ceased.	Returned.
A	16	Slightly atheromatous.	Max. 30	19
			Av. 15.6	8.7
			Min. 3	0
B	3	Moderately atheromatous.	Max. 13	9
			Av. 10	4.9
			Min. 6	2
C	1	Calcified.	Max. 28	14
			Min. 20	10

TABLE IV.—Four Arteries from Amputations.

No.	Artery.	Condition.	Length.	Hours after Removal.	Age of patient. Disease.	Temp.	Difference of pressure at which flow Ceased.	Returned.
43	Fem.	Normal.	7.5 cm.	2	24 Sarcoma.	Stretched 37° C.	4	3
44	Post tib.	Calcified.	11 cm.	2	58 Diabetic gangrene.	37° C.	24	11
73	Fem.	Normal.	7 cm.	1	40 Osteomyelitis.	15° C.	21	16
						Stretched 37° C.	16	6
						37° C.	11	2
						$BaCl^2$ 37° C.	22	10
93	Fem.	Extremely calcified.	8 cm.	1	65 Diabetic gangrene.	18° C.	34	17
						36° C.	37	17
						Stretched 36° C.	28	16

TABLE V.—Surviving Arteries.

Seven Ox Carotids.

Difference of pressure at which flow returned at the different stages of the experiment.

No.	15° C.	37° C.	Stretched.	Adrenalin.	Barium chloride.
72	25	13	9.5	10.5	28.5
75	68.5	14	8	10	15.5
81	50	14	5	7	18.5
82	57	22	6	9	13.5
83	29	8	4.5	8	11
84	39	15	7	7.5	9
90	31	14	6	10	12.5
Max.	68.5	22	9.5	10.5	28.5
Av.	42.8	14.3	6.6	8.9	15.5
Min	25	8	4.5	7.5	9
Four Ox Mesenteries.					
85	52	8	4	6.5	55
86	14	4	4.5	6	18
89	10.5	5	2	6	20
91	24	9	5	8	25
Max.	52	9	5	8	55
Av.	25.1	6.5	3.8	6.6	29.5
Min	10.5	4	2	6	18

VIII. Discussion of Results.

1. *Influence of Varying Internal Pressure.* In our first fifty experiments we considered it important to test the compressibility at different internal pressures, 30, 100, and 150 mm. being used. A glance at the results, especially as given in Table III for the adults' arteries, shows that the difference at these several internal pressures was altogether negligible. Since the experiments on the surviving ox vessels required the use of such great differences in pressure that the internal circulation had to be maintained at 70 mm. Hg, on account of the limited height of our room, it became imperative to make sure that, for living vessels also, their compressibility did not vary with changes in the internal pressure. The following experiment, performed on a surviving ox carotid completely relaxed by stretching at 37° C., demonstrates quite clearly that the height of the internal pressure, under the conditions of our experiments, is without influence on the compressibility of the vessel. The slight differences observed in this experiment are within the limits of experimental error.

Table VI.—Influence of Varying Internal Pressure.

Experiment 93.

Int. Pressure in mm. Hg.	Difference of Pressure in mm. Hg at which flow Ceased.	Returned.
20	11.5	4
40	12	4
60	10	4
80	9	4
100	12	6
120	9	5
140	9.5	5.5
160	10	5

2. *Influence of the Thickness of the Arterial Wall.* Comparative experiments in which the influence of the wall thickness on the compressibility could be tested without complication by any other factor were not attempted. The thickness of the wall varies either directly with the size of the lumen of the vessel or with the state of contraction of its musculature. For this reason the most that can be demonstrated is the combined effect of the thickness of the wall

and the size of the artery. This stands out clearly on comparison of the results obtained from the infant's arteries and from the adult's common carotids. A glance at the summary of Tables II and III shows at once that the small and thin walled infant's vessel can be completely obliterated by very low pressures, the maximum, average, and minimum in all cases lying far below those for adult arteries. The point of resumption of flow was not even measurable with these small vessels, so that only the pressure necessary to produce complete obliteration of the artery was recorded. It seems, therefore, quite evident that, for children's vessels, resistance to compression of the arterial wall does not exist as a practical source of error in clinical blood pressure work.

We believe that the influence of these same combined factors may be seen by comparing the results for the ox carotids and ox mesenteries, when warmed and stretched. In this condition tonus was abolished, and the greater pressure of 2.5 to 4.5 mm. necessary to obliterate the carotid must be definitely related to its thicker wall and larger caliber.

We therefore feel justified in affirming that, other things being equal, the thicker the wall of an artery, the greater is the resistance which it offers to compression.

3. *Influence of Disease of the Arterial Wall.* While it is practically. impossible to study the effect of arteriosclerotic changes on compressibility, uncomplicated by other factors, certain conclusions seem justified from our experiments on adult human vessels from autopsies and amputations. The vessels examined, with the exception of two amputated femorals, all showed slight fatty patches in the intima. These two wholly normal arteries showed a return of flow respectively at 3 and 2 mm. overpressure in the external circulation. These are, of course, altogether negligible quantities. The remaining arteries could be divided into those showing slight atheroma, those showing moderate atheroma with numerous patches of intimal thickening, and those showing calcification.

(*a*) *Atheroma.* A comparison of the results shown in the summary of Table III shows at once that the variation within the group of slightly atheromatous arteries was very great, and that the highest individual readings were above any obtained with much more

diseased vessels, and were even higher than the figures for the single calcified postmortem artery. It is therefore obvious that, whatever influence on compressibility may be exerted by atheroma, it is so far subordinate to the influence of some other factor or factors as to be indistinguishable in our experiments. The other factor, we think we shall demonstrate later, is the state of contraction of the arterial wall. Since one moderately atheromatous vessel gave a reading as low as the lowest normal artery, one hour after amputation and completely stretched at 37° C., we feel that it is probably justifiable to conclude that atheromatous changes are practically without influence upon the compressibility.

(*b*) *Calcification.* It is generally supposed that arteries showing advanced calcification exhibit the most marked resistance to compression. This belief seems altogether reasonable, since, when such vessels are removed and squeezed in the fingers, they feel hard and brittle, and can only be compressed by actual fracture of the chalky plates in their walls. The not infrequent observation of low blood-pressure readings in persons who have nodular calcified brachials, has convinced us in the past that such is not always the case. We were able to examine three arteries showing the most extreme degree of calcification, one postmortem common carotid, and two from amputations for diabetic gangrene, No. 44, a posterior tibial, and No. 93, a femoral. The following table shows the results of all observations on these vessels.

TABLE VII.—Summary of all observations on three arteries showing marked calcification.

	Difference of Pressure in mm. Hg. at which flow	
	Ceased.	Returned.
Maximum	34	17
Average	27.7	14.2
Minimum	20	10

It is evident that the average pressure required to compress these vessels was 5.5 mm. above the average for the slightly atheromatous postmortem vessels. The minimum was strikingly higher, 10 mm., while the maximum was actually 2 mm. below the highest reading from an artery with almost normal wall. It is, therefore,

again evident that even calcification of the most extreme degree has less influence upon the compressibility of the arterial wall than some other factor or factors. The complete explanation of this we hope to obtain by a study of sections taken at different points of these compressed vessels, which we expect to report later. From our rough observation of the behavior of these arteries, however, we think it probable that no such vessels will be found calcified throughout their whole circumference for any considerable distance. It is altogether unlikely, therefore, that any strip of such vessel as much as 10 centimeters long should fail to have soft and uncalcified spots in its wall. Such soft spots may be easily compressed against a calcareous plaque on the opposite side of the vessel, in fact, almost as easily as the normal brachial artery may be flattened out against the humerus. The inspection of these vessels, while undergoing compression, has shown collapse of the vessel in a small area while the rest still stood open, and has convinced us that the foregoing explanation accounts for the apparent disparity between their behavior under the finger and in our apparatus. The importance of examining a segment of sufficient length is greatest in the case of these calcified vessels, and the need for the broad arm piece in clinical work is emphasized from a new standpoint.

It seems safe to conclude that calcification of the arterial wall distinctly increases its compressibility; that the error introduced in this way probably never exceeds 20 mm., and is usually 10 to 15 mm., and that this error is less than may be found from other causes in vessels altogether free from calcification.

4. *Influence of Tonus.* Our studies of surviving arteries from the ox seem to us to demonstrate beyond doubt the predominant importance of the state of contraction of the arterial wall, as a factor in determining its compressibility. A glance at the tabulation of these results shows the enormous resistance to compression of the tightly contracted cold arteries. With the relaxation of the wall produced by warming to body temperature, compressibility is greatly increased, the average fall in pressure obtained in this way being 28.5 mm. for the carotids, 18.6 for the mesenteries. On further stretching to complete relaxation, the arteries could be compressed by comparatively small increments of external pressure.

The greatest difference is seen in one carotid, Experiment 75, which required 68.5 mm. overpressure when cold, only 8 mm. when warmed and stretched. No mesenteric artery when warmed and stretched required more than 5 mm., and no carotid more than 9.5 mm. overpressure.

The most unequivocal results, however, were those obtained after the introduction of adrenalin, and then of barium chloride, into the relaxed arteries. Any change in the resistance to compression produced by these substances, which, simultaneously, evoked a strong contraction of the Meyer strip, must be attributed solely to increased tonus. The effect of such tonus is shown in the following table.

TABLE VIII.—Increased resistance to compression in mm. Hg. produced by

	Adrenalin.	$BaCl_2$.
In seven surviving ox carotids:		
Maximum	4	19
Average	2.3	8.9
Minimum	0.5	2
In four surviving ox mesenteries:		
Maximum	4	51
Average	2.8	25.6
Minimum	1.5	13.5

The constriction produced by barium chloride was much greater than that produced by adrenalin, and very much more lasting. The contraction of the artery was often easily visible. In experiment No. 85 the extreme rise of 55 mm. was so far beyond the next highest rise for the mesenteries of 25 mm., in experiment No. 91, that the question of some undetected error is raised at once. We were unable to discover any source of error, and, therefore, did not feel justified in discarding the result merely because it seemed so extreme.

Another interesting fact, which seems clear from our experiments, is the distinctly greater tonus we were able to evoke in the mesenteric arteries, as compared with carotids. The latter are, of course, more elastic and less muscular vessels, and with their thicker walls showed a uniformly higher reading in the relaxed state than did the former. It seems altogether reasonable that they should show a slighter response to vasoconstricting agents.

From these experiments on surviving ox arteries we feel that the

conclusion is inevitable that the tonus of the arterial wall is by far the most important factor capable of influencing its resistance to compression, and that marked tonic contraction of the artery examined may introduce a considerable error in the clinical measurement of blood pressure. We do not feel in a position, from the small number of successful experiments thus far attained, to set a numerical limit to this error. The carotid of the ox is a decidedly heavier vessel than the human brachial artery, and, in point of size and thickness of wall, the mesenteric is more analogous. If the single extreme result from barium chloride be omitted, we have no figure above 28.5 mm. It seems to us rather unlikely that any degree of contraction of human arteries during life can surpass that which we have obtained with a 2.5 per cent. solution of barium chloride, and altogether inconceivable that anything approaching the condition of the rigidly contracted cold arteries should ever occur in the body. It therefore seems to us reasonably proved that Russell's[1] contention that hypertonic contraction of the arteries, and not high blood pressure, is the cause of the high readings obtained with clinical instruments, has no basis in fact. On the other hand, we must acknowledge that Russell has called attention to a heretofore insufficiently recognized influence of arterial contraction upon our clinical readings. Further studies upon different vessels and different animal species will be necessary to settle finally the exact extent of error from this source.

Because of these striking evidences of the effect of contraction of the arterial wall upon its compressibility, we are of the opinion that herein lies the chief explanation of Herringham and Womack's[2] otherwise unintelligible results. MacWilliam and Mackie[3] have already pointed out the probability of this. Herringham[4] considered that his subsequent sodium fluoride experiment sufficiently answered them, but here altogether foreign conditions were introduced. Arteries after death may evidently pass into a condition of more or less extreme contraction, and require prolonged stretching to overcome it. Such differences between the two brachial arteries, or the carotid and iliac from the same patient, are most easily explicable

[1] Loc. cit. [2] Loc. cit. [3] Loc. cit. [4] Loc. cit.

on the assumption that, because of unequal chilling, or for other causes, one artery became more contracted after death than the other.

As additional evidence of death of an artery in extreme contraction, we would cite an observation made on a surviving ox carotid, allowed to die in position in the apparatus without removal of the barium chloride, with which the last reading was made. The result was as follows:

TABLE IX.—Effect of death of artery in tonic contraction.

Experiment No. 75.

Ox carotid. Internal Circulation 2.5 per cent. $BaCl_2$:

Hours after removal.	Difference of pressure in mm. Hg at which flow Ceased.	Difference of pressure in mm. Hg at which flow Returned.
7	36	15.5
28	74	31

This artery, on examination, felt wholly altered, and resembled rubber tubing or a boiled artery.

IX. THE RESISTANCE TO COMPRESSION OF OTHER ELASTIC TUBES.

A study of all the conditions determining the compressibility of elastic tubes, while it would be most illuminating, involved the solution of more intricate physical problems than we were competent to pursue. The whole conception of elasticity as manifested by the arterial wall, of which compressibility is but one aspect, is greatly in need of clarification; but the practical object of our investigation seemed attainable without a determination of all the underlying causes for our results.

Russell,[1] however, after adducing some rough observations on rubber tubing in an artificial circulation scheme, in support of his contentions, makes the following remarkable statement: "Objection has been taken to these results on the ground that arteries are not rubber tubes. I have made some observations with vessels obtained from the postmortem room, and, so far as I have yet carried these, they seem quite worthless, for the simple reason that the dead

[1] Loc. cit., p. 60.

vessel no longer possesses the *tone* or the elasticity of the living vessel. In fact, the rubber tube is a better substitute for the living artery than the dead one is."

Such an affirmation seemed to challenge criticism and to be well worth a few real observations to prove or disprove. We, therefore, tested rubber tubing of varying thickness of wall and caliber by the same method used for arteries. Not a single sample of tubing could be sufficiently compressed to abolish flow, with the pressure available in our apparatus, hence the point of return of flow could not be observed. The results follow:

TABLE X.—Rubber Tubing.

No.	Type.	Wall.	Lumen.	Difference in pressure in mm. Hg.	Flow.
26 . . .	Black.	2 mm.	7.5 mm.	150	Unchanged.
26A . . .	Black.	2 mm.	5.5 mm.	152	Unchanged.
26B . . .	Black.	2 mm.	4.5 mm.	152	Unchanged.
26C . . .	Black.	1.3 mm.	3.5 mm.	152	Unchanged.
26D . . .	Black.	1 mm.	3 mm.	152	Slightly diminished.
94 . . .	Red.	1 mm.	6 mm.	148	Reduced to 1 drop in 2 seconds.

The tubing selected was the newest and softest obtainable. The smallest we could secure was of thinner wall and smaller lumen than the ox carotids. In the latter, of course, all measurements were wholly relative, depending upon the degree of contraction. A vessel which, when cold, had a scarcely appreciable lumen and a wall several millimeters thick, would, after warming and stretching, have a much greater wall and a lumen more than a centimeter. Definite comparison, however, can be made with a few of the postmortem vessels from Table III, all showing but little atheroma, which we measured. These showed the following striking contrast:

TABLE XI.—Arteries comparable in size to rubber tubing.

No.	Wall.	Lumen.	Difference of pressure in mm. Hg at which flow ceased.
32	1 mm.	6 mm.	18
33	1 mm.	7 mm.	22
34	1 mm.	7 mm.	13

In all the experiments on surviving arteries, after the primary contracture had been overcome, the complete cessation of flow was

produced by pressures not more than 10 mm. above those tabulated for the return of flow; that is, always below 20 mm. With adrenalin tonus their compressibility was not very different, the complete obliteration of the lumen occurring below 30 mm. This is scarcely good evidence that the rubber tube, incompressible at 150 mm., "is a better substitute for the living artery than the dead one is."

The surviving arteries when first examined, cold and rigidly contracted, reacted more like rubber tubing, though none of these failed to compress at 150 mm. Such a condition, of course, is in no way comparable to anything possible in the body.

Under the influence of barium chloride the pressure needed to completely abolish flow was at times surprisingly great, as compared with that at which flow returned. This difference seems worth recording, though all the reasons for it are not yet clear.

TABLE XII.—Surviving ox arteries with barium chloride.

No	Difference of pressure in mm. Hg at which flow	
	Ceased.	Returned.
Carotids:		
72	46	28.5
75	36	15.5
81	88	18.5
82	34	13.5
83	22	11
84	18	9
90	45	12.5
Mesenteries:		
85	104	55
86	27	18
89	46	20
91	40	25
Average	46	20.6

Even these figures are in no way comparable to the resistance of rubber tubes, though they emphasize the complex relations of arterial compressibility. We do not believe that they represent in any way vital conditions, nor that they have any applicability to the practical problem we outlined for this research. The flow which occurred between the point which we have used as our index and the pressure necessary to completely compress the artery was

always a minimal one, by drops. We have convinced ourselves that throughout this range of pressure no pulse wave can pass. It, therefore, in our opinion, represents the persistence of a chink at the outer end of the flattened arterial lumen, through which an occasional drop may escape, and requiring high pressure to absolutely squeeze together. This we also hope to demonstrate later by sections of such arteries during compression. Practically, only the pressure at which flow returns is comparable with the conditions of clinical blood pressure measurement. Furthermore, we question whether any artery during life exhibits such constriction as is produced by strong barium chloride solutions.

The only method by which we have been able to make arteries react like rubber tubes is by boiling them. A large common carotid which compressed at 9 mm. one day and at 13 mm. the succeeding day, after boiling for one minute became incompressible at 164 mm. This was a postmortem artery certainly, but scarcely what Russell had in mind in making his comparison. This immediate and complete alteration of the physical character of an artery by short exposure to high temperature seems to us only to emphasize the essential difference between the arterial wall during life, or for a reasonable time after death, and India rubber.

Two other structures examined by us may be mentioned briefly in closing. An infant's œsophagus was tested and found to compress absolutely at an increment of external pressure of only 1 mm. Hg. This clearly represents the other extreme, a muscular structure with the minimum of connective and elastic tissues, and yielding at once to any deforming force. Intestine was also tested, but fruitlessly, since its lax wall at once collapsed over the end of the outflow cannula.

CONCLUSIONS

1. The arterial wall offers definite resistance to compression.

2. Other things being equal, small arteries with thin walls are more readily compressed than large arteries with thick walls.

3. In infancy and childhood the resistance of the arterial wall is a negligible factor in clinical blood pressure measurements.

4. Arteries as large as the brachial may require only the pressure of a few mm. Hg for the obliteration of their lumen.

5. In adults with normal arteries and a normal range of blood pressure, the arterial wall is a practically negligible factor. It probably never introduces an error greater than 10 mm. Hg in clinical blood pressure measurements, a figure less than the spontaneous variations in pressure from minute to minute.

6. Atheroma, even of considerable degree, is without appreciable effect on the compressibility.

7. Calcification of the arterial wall, when segments longer than 6 cm. are examined, increases only moderately its resistance to compression. The overpressure dependent upon this factor in our experiments did not exceed 17 mm. Hg.

8. In clinical blood pressure determinations, if a wide arm piece be used, and the return of the first fully developed pulse wave be taken as the index, as recommended by v. Recklinghausen, even advanced arterial thickening and calcification probably do not introduce an error of any importance.

9. The only factor determining the compressibility of an artery, which seems capable of introducing an error of real importance in the clinical measurement of systolic blood pressure, is the state of contraction of its walls. It is impossible from our experiments on surviving ox arteries to set definite numerical limits for this in man. From these experiments, however, combined with our study of human arteries, after amputation and postmortem, we feel that a degree of hypertonic contraction of the brachial artery sufficient to cause an error of more than 30 mm. Hg seems improbable, and of more than 60 mm. incredible, during life.

10. The point of return of the pulse after obliteration, not of its disappearance during compression, should always be the criterion of systolic blood pressure.

THE CLINICAL SIGNIFICANCE OF TRANSITORY DELIRIUM CORDIS.

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The clinical studies of irregular heart action which have been reported during the past eight years have shown the great importance of the type of irregularity which has been variously designated as auricular paralysis (Mackenzie), permanent irregularity (Hering), absolute irregularity (Hewlett), and nodal rhythm (Mackenzie). The many names proposed indicate the unsatisfactory condition of our physiological knowledge of this arrhythmia, and yet the irregularity itself has certain clinical features which distinguish it from all others. The most important of these are (1) its permanency in well-established cases, (2) a tendency to extreme irregularity or delirium cordis, and (3) an absence of the auricular waves preceding the ventricular waves on the apex tracing, the venous pulse, the esophageal cardiogram, and the electrocardiogram. During the last five years several writers have noted that irregularities may occur which resemble the typical permanent irregularity except for the fact that they are of a transitory character, and some of these authors believe that such transitory attacks of extreme irregularity may precede the development of the permanent form. For example, Mackenzie[1] details several case histories where "nodal rhythm" was succeeded by normal rhythm, but later became permanent. He also describes a certain type of paroxysmal tachycardia as a transitory "nodal rhythm," but the analogy of this to typical permanent irregularity is less close than is the case in paroxysmal delirium cordis. Hewlett[2] mentions a case where the permanent irregularity was preceded by what seemed to be an attack of delirium cordis. On the other hand, several authors who have described transitory

delirium cordis fail to relate it to the permanent type of irregular heart action. This was true of Cushny and Edmunds,[3] Fr. Müller,[4] Bard,[5] and Hornung;[6] although the latter mentions a case in which the final attack lasted from October 20 to December 13, at which date the patient was discharged with his heart still irregular. It seems probable that in this case the change to a permanent irregularity had occurred under observation.

It is obvious that if transitory irregularity tends to become permanent, it is a matter of both theoretical and practical importance. Of theoretical importance, because the study of such paroxysms might be expected to throw light on the nature of the permanent form of irregularity; of practical importance, because of the necessity for a more guarded prognosis and for greater care in protecting the patient from influences which might hasten the development of the permanently irregular pulse. The criteria by which one may recognize the attacks of delirium cordis to which we wish to draw attention are (1) extreme irregularity, and (2) an absence of the auricular waves on the venous pulse preceding the ventricular waves. Between attacks the pulse is perfectly normal in rhythm and in the form of the venous tracing. The first of the above criteria distinguishes paroxysmal delirium cordis from paroxysmal tachycardia, though the two have some features in common. The second distinguishes it from irregularities due to the frequent occurrence of extrasystoles, where a normal succession of venous waves can usually be found in many parts of an ordinary tracing.

Two of my cases (I and II) have already been reported as instances of paroxysmal irregularity; their further history is of interest in the present discussion. Five of the six were observed at the University Hospital of the University of Michigan, the other being a private case under Dr. Hewlett's care. With the exception of Case I, venous tracings were obtained during the irregular and the regular heart action in each case.

Case I.—*Summary: History of paroxysms of irregularity over many years; first tracings taken after operation; heart apparently normal between paroxysms; paroxysms very frequent and of short duration, ultimately becoming permanent; myocardial insufficiency.* (Case reported by Cushny and Edmunds in 1905.[3])

Mrs. H., aged sixty-four years, was admitted to the University Hospital December 23, 1901, for ovarian fibroid. She was operated upon December 24.

Anesthesia (ether) for one hour and twenty minutes. Condition at end of operation was good; pulse 90 beats per minute, with no indication of irregularity. There was persistent nausea until the 27th. On the 25th and 26th the pulse rate varied between 90 and 100, with frequent periods of irregular action, as noted by the nurse. On the 27th there were three irregular paroxysms, at 8 A.M., 2 P.M., and 8 P.M., when it was impossible to obtain accurate counts at the radial. On the 28th and also on the 29th frequent tracings were taken at the radial with a Jacquet sphygmograph. These showed distinct periods of irregularity lasting in some cases only a few minutes, and then the heart suddenly would become regular again. On December 30 the nausea and vomiting stopped, with a general improvement. The irregular periods became less frequent and were confined almost entirely to the night. The patient would wake up suddenly, and the heart at once became very irregular. On January 11 the heart was very irregular during the night, but became regular toward morning and remained so until January 18, when she was discharged. The patient reported back to the hospital that the night following her discharge the heart action was very irregular.

The tracings taken during these paroxysms of irregularity, while they lack the confirmatory evidence of the venous pulse, show a typical delirium cordis. A number of large pulsations occurred at irregular intervals, and had interspersed among them smaller pulsations, sometimes singly, at other times in twos or threes or in groups of larger numbers.

The patient stated that she first noticed the irregularity twenty years before during an illness, and that since then it had occurred whenever she was ill, excited, or exhausted. Vomiting, to which she was occasionally subject, was always followed by irregularity. The tendency to irregularity seemed to increase about ten years before the operation, as she observed that less important occasions would give rise to it than previously.

Examination of the heart during the patient's stay in the hospital showed no enlargement of cardiac dulness, no murmurs, and no objective signs of embarrassed circulation either during the irregular periods or in the regular intervals between. Clinically, then, nothing was found but alternating periods of regularity and irregularity, with no symptoms of heart failure during the irregularity nor any apparent lesion in the heart itself which might be responsible for this sudden inception of an abnormal rhythm.

In 1905 a letter was received from the patient stating that for two years after the operation she suffered very little from her heart, but then some overexertion gave rise to cardiac irregularity again, and for the last year very slight exertion or exposure to heat or cold has induced an attack.

The patient was seen on December 7, 1909, at which time she stated that she had been suffering from serious heart symptoms for some time, and that her heart was now continuously irregular. A few years before she had had sudden pain about the heart and in the left shoulder, and she had since had more or less pain in both arms. She was now more or less continually short of breath, this becom-

ing worse if she was tired or excited, and was also worse on exertion. At times the shortness of breath came on in spells. She had smothering attacks at night, at which times she felt that she could not get her breath and had to sit up. When walking, she frequently got dizzy and things became black before her face. One year before her feet were badly swollen, but this had practically disappeared. She did not take cold easily. She had gradually been losing weight and her appetite was variable.

Examination at this time showed an emaciated woman inclined to dyspnea on slight exertion. The apex beat was in the fifth intercostal space in about the mammary line. The right border of the heart was 1 cm. to right of sternal margin. There were no heart murmurs. The second sounds were of normal intensity. Heart action was very irregular. The arteries were thickened and tortuous, the liver was moderately enlarged and tender to the touch. The tracings taken on this date showed the typical features of a permanent irregularity.

Case II.—*Summary: Mitral stenosis; first paroxysm observed after influenza; later ones induced by excitement or exertion; about seven paroxysms in five months; ultimately became permanent; numerous emboli, which finally caused death.* (Case reported by Dr. Hewlett.)

Mrs. B., aged fifty-five years, was first seen in February, 1908. Her family history was negative. She had never had acute articular rheumatism. In June, 1906, she had been treated for "heart disease," which had become so bad a month later that she had been unable to sleep in a recumbent position on account of dyspnea. Since then she had had several breaks in compensation, with dyspnea, cardiac distress, and at times slight edema. In the intervals the compensation had been fairly good. When first seen, there had been an epidemic of influenza in the household, and she was suffering from the usual symptoms of this infection. In addition she presented the typical signs of a mitral stenosis.

Examination at this time showed a pulse of 80 per minute and perfectly regular. The mitral stenosis murmur was of a marked presystolic type, with little if any rumble in early diastole. Three days later after her temperature had fallen to normal, she complained of precordial distress, and felt unusually weak. The heart action was found to be absolutely irregular and about 102 beats per minute. The mitral murmur had completely changed its character. Its presystolic accentuation had disappeared, and it was now loudest just after the second sound, and in the longer diastolic intervals it practically disappeared before the occurrence of the first sound. The following morning the heart action was again perfectly regular and 85 beats per minute, and the murmur had returned to its customary presystolic type. The precordial distress and general weakness had passed away.

In the next five months the patient had about seven of these paroxysms of cardiac irregularity, in three of which tracings were made which showed the characteristic absence of "a" waves. These attacks seem to begin abruptly and were induced especially by emotional disturbances, *i. e.*, by seeing a dog

nearly run down by a street car. Other attacks seemed to follow physical exertion. The attacks usually lasted during the day and passed off during the following night, the termination being associated with sweating. During the paroxysms the patient felt weak, short of breath on exertion, and suffered considerable distress from cardiac palpitation. Examination of heart during paroxysms showed a slight enlargement of the cardiac dulness and the change in the diastolic murmur already described. Between attacks her venous pulse was of the normal type, with fairly prominent auricular waves.

In the latter part of May, 1909, the heart action became absolutely irregular, and the murmur permanently changed to the character it had shown during the former paroxysms. There was marked dyspnea on exertion, with considerable cardiac distress, the general symptoms being less, however, than they were during the transient periods of irregularity. Death occurred by embolism of the abdominal aorta and gangrene of the legs.

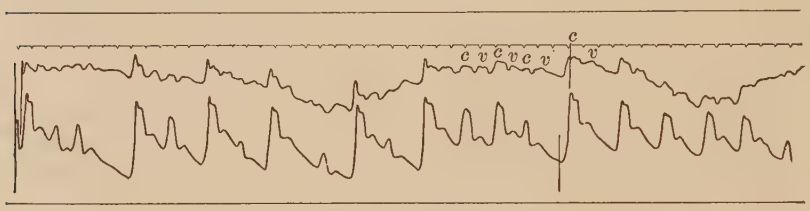

Fig. 1.—Case III. Paroxysm of irregularity on October 11, 1908. No auricular waves on the venous tracing.

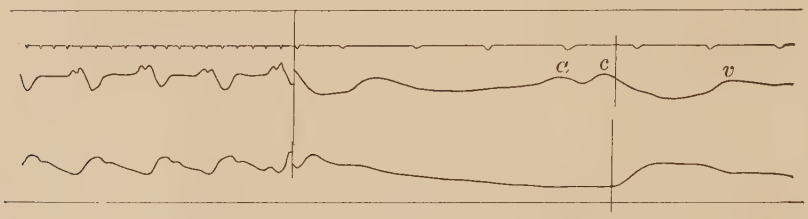

Fig. 2.—Case III. Normal pulse of October 17, 1908.

Case III.—*Summary: First paroxysm observed after anesthesia; heart apparently normal between attacks; occasional paroxysms for several months, after which the irregularity became permanent and the patient showed the symptoms of myocardial insufficiency.*

Mr. P., aged sixty years, entered the surgical clinic of the University Hospital on October 8, 1908, and was operated upon on the 10th for a hydrocele. Very shortly after coming out of the anesthetic he developed a marked cardiac irregularity and was immediately transferred to the medical ward. The history which was later taken threw no light on the condition, the family and personal history being in every respect normal. Tracings showed a well-marked delirium

cordis, with no "a" waves on the venous pulse (Fig. 1). During the attack the patient was obliged to sit propped up in bed in order to avoid a most distressing dyspnea. The heart outlines during the attack differed in no respect from those present on his admission to the surgical service. There were no murmurs either at base or apex. The first sound at apex was faint, but distant and somewhat muffled, the second sound weak. The second aortic was of about the same intensity as the second pulmonic. On the following day the pulse became regular, and tracings showed a perfectly normal picture (Fig. 2), but on the 12th the pulse again became irregular and the tracings were the same as those taken shortly after his admission to the medical ward. He had several paroxysms during his stay, but on being placed on digitalis these attacks ceased, so that he

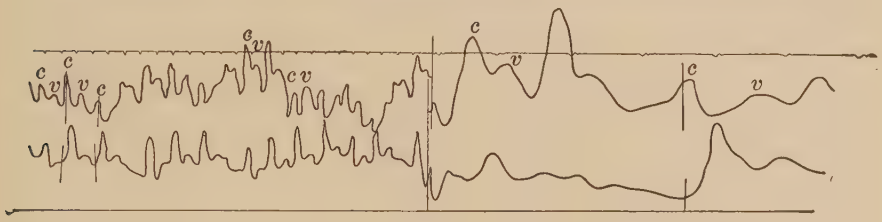

Fig. 3.—Case III. Tracing during the permanent irregularity, June, 1909.

was discharged on October 17 with a regular heart action and apparently well. Letters from the physician who later attended him, Dr. Backus, of Fayette, Ohio, stated that early in December, following several more paroxysms, the pulse became permanently irregular. On June, 4, 1909, he was re-admitted to the hospital with a permanently irregular heart of the ventricular type as shown by venous tracings (Fig. 3). His shortness of breath was much increased, there was some cyanosis with a very troublesome cough, but no essential change in outlines of the heart. The apex beat was now of a very heaving character, spreading over the entire precordium. He left the hospital a week later very little improved and the heart action still showing the characteristics of a permanent delirium cordis.

Case IV.—*Summary: Emphysema; myocardial insufficiency, with enlarged heart; only one paroxysm observed, then became permanent.*

Mr. W., aged fifty-nine years, was admitted to the out-patient medical clinic on January 6, 1907, complaining of shortness of breath on exertion, swelling of the lower extremities, and a very severe persistent headache. The family history was negative except for a vague account of cardiac trouble in the parents. His personal history was negative except for occasional swelling of the feet in the evening and periodic headaches, for which he had taken large quantities of acetanilide. For the last seven years these symptoms had progressively increased.

Examination: Thorax short, round, approaching a barrel chest type. Slight cyanosis of head and extremities. No apparent dyspnea. Veins of arms and chest full, neck veins not prominent, systolic pulsation not marked. Percussion

showed heart boundaries apparently not enlarged. Apex beat poorly seen, felt in the fourth intercostal space inside nipple. At apex, first sound distant, muffled, followed by prolonged rather harsh blowing murmur transmitted outward but not upward. Murmur not heard in axilla or back. Sounds at base very feeble, aortic scarcely audible, radial fairly full and rather compressible, artery moderately thickened. Systolic pressure, 115; diastolic, 75. Venous tracings taken at this time showed a regular heart with well marked "a-c-v" rises on the venous pulse.

On the 11th of the same month he returned to the clinic complaining of another attack of intense headache, rapid pulse, and palpitation of the heart. On examination, there was nothing marked except the extreme irregularity of the radial pulse and slightly increased cyanosis. Tracings taken showed a typical delirium cordis with the ventricular type of venous pulse.

On the 15th he was seen at his home, and apparently had completely recovered from his attack. The pulse was perfectly regular, both as to rate and intensity, and the subjective symptoms were those present on first visiting the hospital.

He returned to the clinic on March 1 with a partial return of the symptoms which he had had on January 11, the dyspnea being a little less, but with marked swelling of the feet. The pulse at this time showed no abnormality.

On December 12, 1909, he was seen again. He complained of dyspnœa on unusual exertion, spells of nervousness and occasional palpation, but on the whole he felt better than he had at any time during the past year. More tracings were taken, which showed the positive pulse with a fairly well-marked irregularity of the radial. He said that his pulse had been irregular ever since he was last seen (March 1, 1907).

Case V.—*Summary: Arteriosclerosis; myocardial insufficiency, with enlarged heart; numerous paroxysms observed; later became permanent.*

Mr. S., aged sixty-eight years, was admitted to the medical clinic of the University Hospital, April 9, 1909, suffering from weakness, palpitation, and shortness of breath on exertion. His family and past history were negative except for several slight attacks of inflammatory rheumatism at an early age. The trouble which brought him to the hospital began about two years previously as gradually increasing weakness and inability to undergo any exertion without a consequent period of breathlessness, which sometimes assumed such proportions that the patient became very much alarmed. His weight dropped during the winter over forty pounds, and was gradually going down during the early spring. He found that while in bed the palpitation of the heart was much lessened, and as a consequence he had been more or less in a recumbent position for a month or so. The examination showed an emaciated man with wasted musculature and pale muddy complexion, and in general he presented the picture of one suffering from a severe constitutional disturbance. His apex beat was heaving in character and well localized in the sixth intercostal space just outside the mammary line and about 11 cm. to the left of the median line. The area of cardiac dulness was very difficult to outline accurately, but extended about 1 cm. beyond the right border

of the sternum. The upper border was apparently in the third intercostal space and the left boundary about 12 cm. from the middle of the sternum in the fourth intercostal space. The first sound at the apex was somewhat impure, but without any definite murmur. The second pulmonic was louder than the second aortic, but neither was markedly accentuated. There was marked beaded sclerosis of the radials and hard, tortuous brachials and temporals. When the

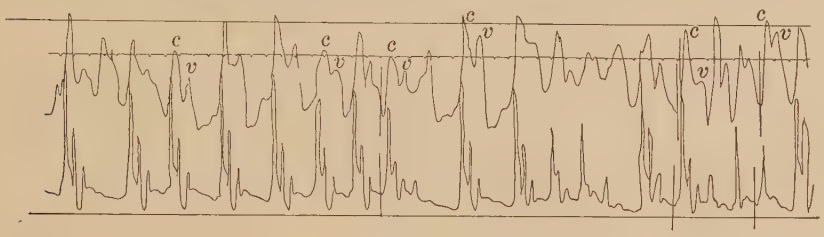

FIG. 4.—Case V. Attack of delirium cordis on April 14. Note that the venous pulse is of the positive type, beginning almost simultaneously with the radial.

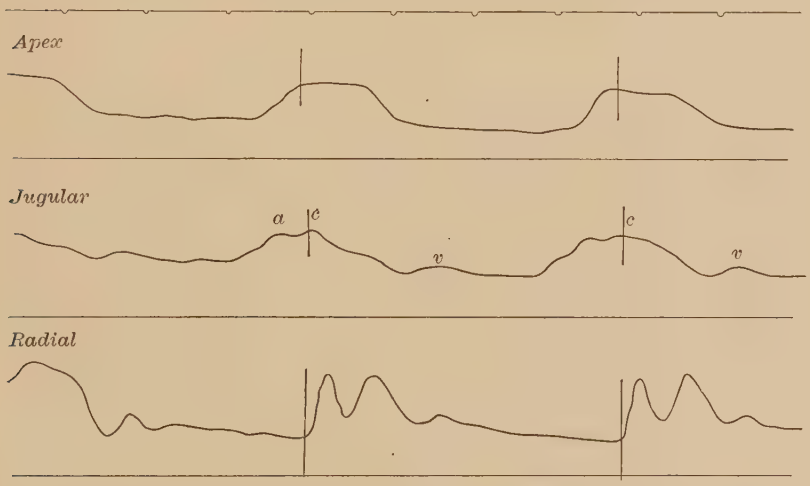

FIG. 5.—Case V. Taken a few minutes after Fig. 4. Note that the pulse is now regular and that the venous pulse begins distinctly earlier than in that figure, owing to the presence of an auricular wave.

patient first came to the hospital his pulse was regular as to rate and intensity of beat, but on the third day after admission it was noticed to be extremely irregular and intermittent. Before the apparatus could be prepared to take tracings from the radial, this irregularity had disappeared, and when the tracings were finally taken they showed a perfectly regular action, the rate being about 98 to the minute, with well marked "a" waves on the venous record. On the 14th

the pulse again became slightly intermittent, and while the apparatus was being applied to his wrist the heart became extremely irregular and remained so while two tracings were taken (Fig. 4), and then quite suddenly and without any apparent cause became perfectly regular again (Fig. 5). Several other sets of tracings were taken during the regular and irregular intervals (Fig. 6). In each case when the cardiac action was regular we had a normal inception of the rhythm, the "a" wave slightly preceding the ventricular systole, with the "c" and "v" waves following in order, while the tracings taken during the periods of irregularity showed the ordinary characteristics of the absolutely irregular heart—no "a" wave whatever and the large "c" and "v" waves which occur in

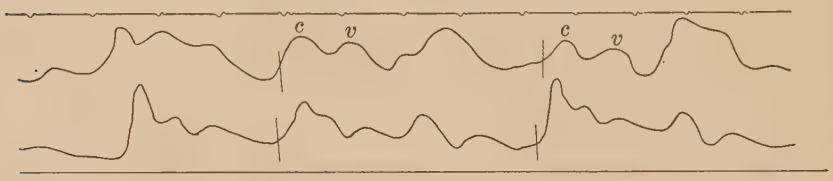

Fig. 6.—Case V. Tracing during the irregularity of April 15. The pulse is very irregular and the auricular waves are absent.

this condition. During the paroxysms of irregularity he showed a pronounced dyspnea, with some slight cyanosis and all the subjective symptoms of an embarrassed circulation. On closer questioning he stated that he had had several attacks of a like character previous to his admission. He was discharged on April 16, his heart action being perfectly regular at the time. Dr. Hargrave, of Palo, Michigan, who attended him on his return home, stated in a letter received November 24, 1909, that the arrhythmia has now become permanent, with a change for the better, however, in the subjective symptoms under complete rest and large doses of strychnine sulphate.

Case VI.—*Summary: Several paroxysms of irregularity following operation; heart apparently normal between attacks; up to present has remained regular.*

Mrs. H., aged forty-two years, was admitted to the gynecological service of the University Hospital on October 29, 1909, suffering from carcinoma of the uterus. There was nothing in her family or personal history which caused any suspicion of cardiac trouble, but on November 4, two days after operation, her pulse became very irregular and intermittent. This was unaccompanied by any symptoms on the part of the patient, and as it lasted only a few hours, no particular notice was taken of it. She had another period of irregularity on the 6th which was very transitory, but on the 7th, upon the appearance of the irregularity, tracings were taken which showed a moderate degree of irregularity of the radial pulse, with a marked ventricular venous tracing. The heart when examined on her admission to the hospital was perfectly normal in every respect, no enlargement and no murmurs. An examination of the heart was made and an orthodiagraph taken

during this period of irregularity, but no abnormalities other than the arrhythmia could be detected. At no time during any of the paroxysms did she complain of any distress, nor could she remember ever having had any irregularities previous to the present ones. Ten days later she was discharged from the service, her pulse in the meantime remaining perfectly regular, the tracings taken showing no change from the normal whatever.

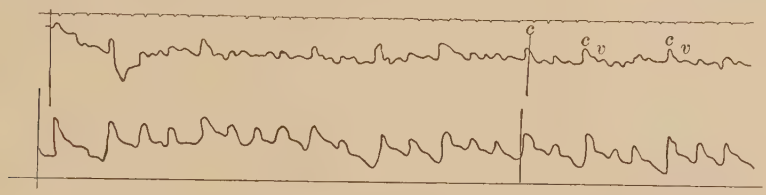

Fig. 7.—Case VI. Paroxysm of delirium cordis on November 7.

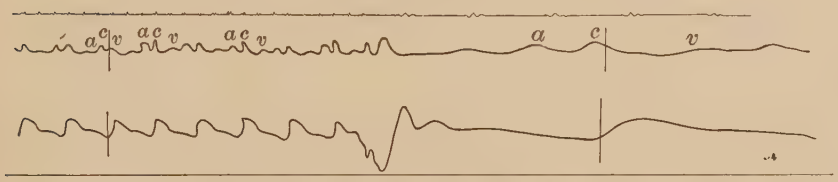

Fig. 8.—Case VI. Regular and normal heart action five hours after the preceding tracing was taken.

Remarks. We have, then, six cases of transitory irregularity. Venous tracings were taken in five of these, and they showed the typical absence of "a" waves during the paroxysms and perfectly normal tracings during the periods of regular heart action. Five of these cases subsequently became permanently irregular, and the sixth was observed for too short a period to be certain that it, also, would not become permanently irregular in time. Venous tracings taken after the pulse had become permanently disorderly showed the ordinary characteristics of that condition.

These patients were all above forty-two years of age, ranging between that and sixty-eight years. The number of paroxysms and the duration of each varied in each case, the greatest number observed occurring in Case V, most of which, however, were of short duration. The exciting causes of the paroxysms in Case I were several, excitement, exhaustion, and vomiting being the most prominent. Emotional disturbances in Case II would frequently

bring on attacks of irregularity, although she, too, like the preceding, would suffer a paroxysm when she became unusually exhausted. The attacks in the remaining cases came on from no apparent cause, some of the paroxysms in Case V occurring while he was resting quietly in bed. Two of the cases developed their first irregularly after operation, neither one of which revealed any abnormal cardiac condition on initial examination. The time which elapsed between the first observed attack of irregularity and the establishment of a permanent delirium cordis could not be ascertained very definitely in each case, but the longest time was approximately fifteen months and the shortest three months. Case I, however, believed that she had had such attacks for twenty years.

Physical examination of the heart showed one case of mitral stenosis. Two patients had large hearts with myocardial insufficiency on the first examination, one of these having a systolic murmur presumably due to a relative mitral insufficiency. In the remaining three there were no abnormal signs previous to the first attack or between the paroxysms, but later, when one of these became permanently irregular, the heart was slightly larger. In Case VI the orthodiagraph showed no change in the size of the heart during a paroxysm.

The nature of this irregularity is still a matter of conjecture. In all these cases the attacks developed and ceased suddenly. This, together with the complete change in the character of the venous pulse, leads one to assume that in some way there had occurred an abnormal inception of the cardiac rhythm. Two main theories as to the nature of this abnormal rhythm are held at present. These are (1) the "nodal rhythm" of Mackenzie,[1] and (2) auricular fibrillation (Cushny and Edmunds,[3] Lewis,[7] Rothberger and Winterberg[8]). According to the first theory, these attacks of transient irregularity are caused by a change in the point at which the cardiac rhythm is initiated, shifting from the remains of the sinus venosus to the persisting portion of the primitive tube farther down, *i. e.*, the auriculo-ventricular node. When this occurs, we have the impulses travelling both ways, up and down the His bundle, with a consequent simultaneous contraction of auricles and ventricles. According to the auricular fibrillation theory, the auricles pass into a state of fibrilla-

tion. In this condition coördinate auricular contractions cease and the separate portions of the muscle fibrillate, so that as an organ the auricles have ceased to beat and remain practically motionless. In this way an irregular discharge of impulses from auricles to ventricles occurs, and we have the ventricles beating in a more or less disorderly manner, with no evidence on the venous tracing of any auricular contractions.

Conclusions. Of six patients in whom transient attacks of delirium cordis were observed, five eventually developed the permanent type of irregularity. Many features of the attacks themselves would suggest a nervous condition, especially the onset under excitement and the complete recovery between attacks with no demonstrable heart changes. The prognosis, however, should be guarded and efforts made to avert the onset of a permanent irregularity, which is practically always accompanied by symptoms of cardiac insufficiency.

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DISCUSSION.

Dr. Joseph H. Pratt: I have now under observation a case of the type described by Dr. Hewlett. Unlike his cases, my patient had no dyspnea, even during the attacks, and no other evidence of heart disease. The closeness with which it simulated a cardiac neurosis is the point I wish to emphasize. The patient is aged sixty-three years. He is strong and vigorous, but is of nervous temperament, and has from time to time neurotic manifestations, which have been readily relieved by simple measures. For the past two years he has been troubled by the accumulation of gas in the intestine, and when he first consulted

me, in December, 1909, he complained only of indigestion. He has had six or seven attacks since last October, characterized by an irregular action of the heart, of which the patient is conscious, and a very weak and irregular pulse. Sometimes the rate is slow, sometimes rapid. Prostration, loss of appetite, eructations of gas, and a sensation of oppression in the abdomen have occurred during the attacks. The usual duration has been from six to twelve hours. The onset and end of the attacks occur suddenly. Between the seizures he feels perfectly well except for occasional symptoms of nervous dyspepsia. He is easily worried by affairs of business and at times has insomnia. The heart was not enlarged on percussion, and this finding was verified by an examination with the orthodiagraph. The heart sounds were clear and loud. The aortic second was not accentuated. The radial pulse was slow and regular. The maximum blood pressure was 130 mm. Hg. The peripheral arteries were not sclerosed. During the attacks Dr. C. C. Day, the attending physician, has never observed shortness of breath or cyanosis. I had the opportunity to see him in one attack. The pulse was weak and absolutely irregular. At times it was almost imperceptible. The rate varied greatly. In the middle of the attack I found it about 100. Later, short periods of rapid action occurred, lasting thirty seconds or less. I counted thirty-eight beats in fifteen seconds. A tracing showed the jugular pulse to be of the ventricular type. The heart sounds were very weak and at the end of the attack inaudible. There was slight dilatation of the heart to the left. After the attack the heart quickly returned to its normal size, the pulse became regular and of good volume, and the wave reappeared in the jugular tracing.

Dr. Walter B. James: I think the study of irregular hearts by modern means and the classification of the findings is entirely unsatisfactory. Any classification of the classes of permanent irregularity of the heart that is characterized as temporary is certainly not above suspicion. In my studies of 150 cases and cardiograms has left me with the conviction that arrhythmia forms an important group of cases which has not been subdivided satisfactorily. There is no question whatever but that a great number of these cases depend upon an irregular auricular fibrillation. I believe that the use of the electric cardiograph is the only way to determine whether this is the case or not.

As to the permanency of the lesion we must also say that auricular fibrillation is necessarily associated with permanent irregularity of the heart. I have seen one case of acute lobar pneumonia in which, during the patient's convalescence, he had an irregular heart, a heart which one could not diagnosticate by the ordinary clinical means. The electrocardiograph, however, showed a definite fibrillation of the auricle. Further on in his convalescence this irregularity was lost, and he went from the hospital an ordinarily normal individual. These observations prove that our classification of irregularities of the heart is not satisfactory. Some cases are certainly due to fibrillation. It is not possible by ordinary means, clinical means, to determine whether the irregularity of the

heart is due to fibrillation, or to tell whether it will be a permanent irregularity or not.

Dr. Richard C. Cabot: I should like to ask Dr. Hewlett the ages of his patients.

Dr. Isaac Adler: I have seen quite a number of cases such as Dr. Hewlett has just described. Having no electrocardiograph at our disposal, we have found it possible to differentiate between myodegenerative and purely nervous affections of the heart by other means. I do not wish to go into any details at present, but simply state our mode of procedure. An irregular pulse, depending mainly on purely nervous influences, is very apt to become regular, or nearly so, on exercise. The hearts whose muscles are fairly sound diminish in size when viewed with the orthodiascope after hard work. Under the same conditions the blood pressure in purely nervous cases, though somewhat uncertain, is usually increased. We therefore count pulse carefully, take a sphygmogram, if advisable, take the blood pressure with the Recklinghausen or Erlanger, and take a diascopic tracing. The patient is then set to work at the ergograph; 4000 kg. in four minutes we have found to be about the usual work of a healthy subject. After work at the ergograph a new set of tracings is taken, and by this comparison the diagnosis whether merely or largely nervous influences are active, or whether a myocarditis or other myodegeneration is present, can be made very frequently with sufficient accuracy.

Dr. Hewlett: I agree with Dr. James that it is difficult at present to classify this form of irregularity. For this reason Dr. Fox chose to speak of it as transitory delirium cordis, which is not a very satisfactory term, but does not commit one to a theory as to the underlying pathology. From our experience there is a decided tendency for such transitory attacks to become converted into a permanent irregularity. One should therefore be cautious in giving a very favorable prognosis. One of our patients had a paroxysm of delirium cordis after a minor operation, and when he left the hospital he appeared to be perfectly well in every respect. At the present time, however, he is completely incapacitated by a permanent irregularity with cardiac insufficiency.

In answer to Dr. Cabot, all of these patients were past forty years.

A CLINICAL METHOD OF ESTIMATING THE COAGULATION TIME OF THE BLOOD.

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TORONTO, CANADA.

Many different methods have been employed for estimating the coagulability of the blood. In all these methods no attempt is or can, of course, be made to actually measure the time or extent of the coagulation when the blood is surrounded by normal tissues and is circulating in a normal manner, for under such circumstances it does not coagulate at all. The aim is always the testing of the coagulability of the blood under certain unnatural surroundings, and as these surroundings differ in different methods, the results obtained can only be compared in the most general way. Thus, by one method healthy blood may coagulate in two minutes, and by another in fifteen, and yet by each method the conclusion may be arrived at that the coagulation time is normal.

Among the various methods which have been advocated for the measuring of the coagulation time of the blood some, such as that of Brodie and Russell,[9] and especially Addis' modification of it,[3] appear to give very constant results, but such apparatus is too complicated and elaborate for ordinary clinical use. Among the simpler clinical methods, probably that of Wright has been used more widely than others, but in the hands of different observers has given very inconstant results. His method consists in filling several fine glass tubes with blood and keeping these at a temperature of 37° C. in a vessel of warm water, and then at intervals blowing out the contents of each tube until one is found to have coagulated. With this method, coagulation occurs normally in about two minutes, and in abnormal conditions may take place in thirty seconds, or even less. Many

men find the method to give reliable results, but an objection, which naturally arises, is that the whole operation is so quick that any delay in manipulation would markedly change the findings. Thus, Addis[3] says that it took him nearly thirty seconds to fill the tubes and introduce them into the water bath. Turner[1] made over 1000 observations with the method, and while the average coagulation time was two minutes and forty seconds, he says that differences of *two* minutes occurred in the time of the same individual in successive punctures.

Many other methods have been introduced for clinically measuring the coagulability of the blood, and a mere list would be of no value, so is here omitted.

In 1904 Sabrazés,[7] following in the footsteps of others, published a method of using fine glass tubes, which were filled with blood and then broken across at half minute intervals, and the broken ends slowly separated. When a thread of fibrin appeared between the broken ends, coagulation was said to have occurred. In 1906 Geneuil[8] published a thesis on coagulation of blood, in which he used Sabrazés' method extensively, and in the *British Medical Journal* of 1907 a paper appeared, by J. P. McGowan,[4] advocating the same method (as regards the use of glass tubes), and it has been with tubes as made for McGowan, in Edinburgh, that we have worked. Addis,[3] who has written extensively upon the subject of coagulation, in reviewing the different methods, came to the conclusion that the end-point adopted here, viz., the moment when a thread of fibrin appears between the broken ends of the tube, is freer from errors of technique than any other of the simpler methods employed. He found, in a series of 256 estimations, that the average difference in the coagulation time in each of tubes filled at the same time and kept under the same conditions was thirty seconds; and, as the average time of coagulation was eight minutes, the margin of error was small. Our results fully bear out this finding. Sabrazés kept his tubes in an apparatus consisting of two glass boxes, the lower of which contained hot water or ice, and the upper the tubes and a thermometer. He says that if the temperature in the upper chamber be too high, one may lift the vessel, so as to let in cool air, or carry it to an open window; if, on the other hand, it be too low,

the lower chamber may be heated with a lamp. The lid had to be taken off every time that a tube was removed for breaking, moreover, so the keeping of the tubes at a constant temperature seems full of difficulties. McGowan used no apparatus for maintaining the temperature at one point, and says that while for accurate work the tubes may be kept near a thermometer, for clinical purposes a temperature between 15° and 20° C. does not matter. This, as will be shown later, is very misleading, as, roughly speaking, each degree between 15° and 20° C. makes a difference of about one minute in the coagulation time.

Addis, finding that the maintaining of a constant temperature was so important, introduced a thermostat for this purpose. We have used his apparatus considerably and find that it does this, but is of bulky size; and, moreover, in our hands is inconvenient in that the tubes must be put into the apparatus vertically through very small holes, and hence must be first sealed, which takes considerable time —during which they are exposed to the room temperature. However, Addis, using the apparatus, got results that were very constant, and with which our findings closely correspond.

During the first 400 or so estimations we used no apparatus to keep the temperature the same, but the tubes, after being filled, were laid alongside of a thermometer and kept there until the end of the experiment. The results were then plotted out on a chart in order that one might by reference to this chart judge of the probable clotting time in any future case. And this method may be useful for rough clinical work, but for more accurate work, and for comparing a case's condition from time to time it is much better to always work at one temperature, and this may be conveniently done by using a simple portable apparatus, which consists of the following parts:

Apparatus and Method. Thin glass tubes, 1.5 mm. in diameter and about 7 inches in length, are used. A pint Thermos bottle is employed, and its ordinary cork is replaced by a rubber one perforated in three places. In these perforations rest two brass tubes, seven inches long and just large enough in caliber to easily hold the glass blood tubes. The third perforation in the cork contains a thermometer. The apparatus rests on its side on a special stand, which prevents it from rolling about.

The bottle is filled with water at the temperature at which it is desired to work, say 20° C., and the cork is put in position. The temperature of the contents will remain for fully an hour at the same point in a room of 55° F., or more.

The back of the finger or thumb near the nail is cleansed with soap and water and then with alcohol. As soon as it is dry, the digit is wrapped about loosely with a piece of twine, and at once punctured, the exact time of puncture being noted. Two glass tubes are partially filled from the same drop, the blood being made to run nearly to the far end of each, and each, as filled, is placed in a brass tube of the thermostat—the first in that to the left, and the other in that to the right. Then the protruding ends, which are the ends at which the blood entered the tubes, are sealed at one's leisure with a spirit lamp. In about five minutes the first tube is drawn out of its container by the left hand (which is covered with a thick glove, in order that the heat of the fingers may less affect it) and touched with a glass file and broken across between one's fingers and thumbs, and the broken ends are slowly separated. Probably the blood column also breaks across sharply, if one may so speak of a column of fluid. The tube is at once replaced in the thermostat. In half a minute the second tube is removed and treated in the same way. Soon, on breaking the tube across and separating the ends, a thread of fibrin appears between the broken ends. At once the tube is broken further on, and probably the thread of fibrin again appears. Very rarely a thread appears at the first break and not at the next one. This would be counted as a negative finding, and the tube would at once be replaced in the thermostat and tried again in fifteen seconds. If one be careful to begin the breaking at the first blood which entered the tube, such a thing seldom happens. One of the alternating tubes having given a positive finding, the other one almost certainly will do so in the next half minute, but if not, then usually in the next. With quick working one can try them every quarter of a minute, but the half-minute intervals give more time to make sure that a given tube has really coagulated, as it can be broken several times before the next one is due.

More recently we have been confining our attention to tube No. 1, and only when it shows a coagulum do we try No. 11 as a control.

This change was made at Professor Brodie's suggestion, as the first tube can be more accurately timed, and also contains the most normal blood, as the later the blood flows from the wound, the more readily does it coagulate. This was shown by Addis, who found that at 18.5° C., using his special apparatus, the blood which first flowed from a puncture coagulated in seven minutes and fifteen seconds, while that drawn from the same wound a minute later took five minutes and fifteen seconds, and after two minutes the blood coagulated in three minutes and forty seconds. Similarly, we found that at 20° C. the blood from the first drop coagulated in nine minutes, and that from the same wound two minutes later in five minutes and forty-five seconds. Of course, the wound had been carefully wiped dry and clean before the second drop was taken. On another occasion, under similar circumstances, the respective readings were eight and five minutes for the first and second drops, at a two minute interval. The blood must flow easily from the puncture, as we find that any squeezing of the part produces a blood that coagulates with greater speed. The blood that first flows from the wound is always used, and the tubes are filled as rapidly as possible. It is easy after a little practice to have both tubes filled and safely in the thermostat within thirty seconds of the time of puncture.

The so-called McGowan tubes are 1.5 mm. in diameter, and these are what we have worked with, but Addis and Sabrazés used tubes of 1 mm. only, and their readings are about one minute faster than ours. Sabrazés states that slight variations (between 0.8 and 1.2 mm.) in the size of the tubes makes no difference in the results, and again and again we have selected the largest and smallest tubes from a lot and have found them to give practically the same readings.

The temperature of the room in which the experiment is carried out seems to have a slight influence in the results, and when the thermostat is at, say, 20° C., one looks for a slightly longer reading in a cool than in a warm room. This is probably accounted for by the cooler condition of the tubes before use, of the finger punctured, of the glove worn by the operator, etc. To lessen the influence of the first source of error here the tubes should be placed in the thermostat for about a minute before using them in a cool room.

The temperature at which the tubes are kept during the experi-

ment has a most marked influence upon the coagulation time, and one must absolutely disagree with McGowan when he states[4] that "for clinical purposes, the providing of an apparatus for keeping the blood at a uniform temperature seems to be superfluous, as from my readings, done at room temperature, which varied from 15° to 20° C., there was no change in the coagulation time corresponding to the elevation or lowering of temperatures within these limits." In Figs. 1 and 2 it will be seen how greatly the temperature

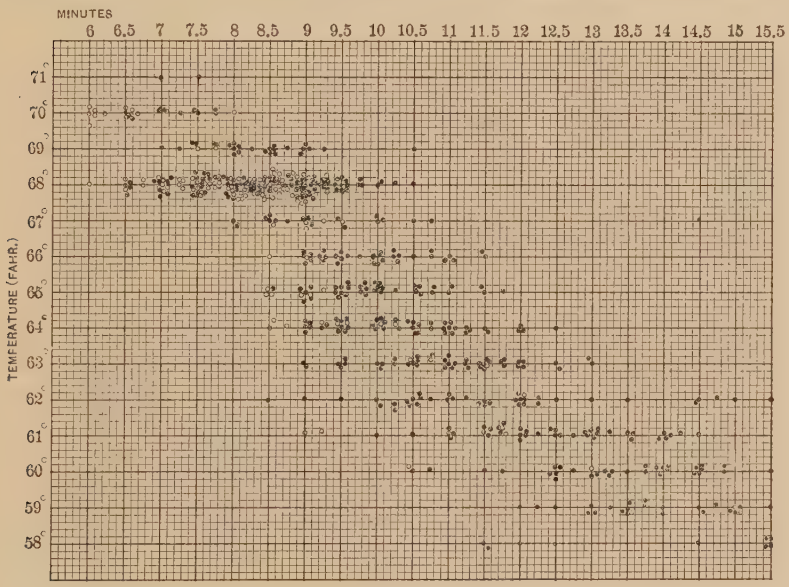

FIG. 1.—605 coagulation measurements. The solid dots represent measurements of the author's blood, and the circles those of other healthy individuals.

affects the readings. In Fig. 1 the black dots represent the writer's coagulation times, and the red those of different, apparently healthy, individuals of different ages and sex. In Fig. 2 these results are averaged. They show that, roughly speaking, each degree between 15° and 20° C. makes a difference of about one minute in the coagulation time. As already said, for rough clinical work, with the aid of a thermometer and such charts as these, an estimation of the coagulation time may be made and compared with the average results for that temperature.

At any given time the coagulation time of an individual, as measured by our method, varies very little, showing that the experimental error is small. It is quite unusual to find in several tests made one after the other in rapid succession on blood from the same individual that the readings vary more than one minute, and more often they come out exactly the same. But on another day, at the same hour and at the same temperature, there may be a difference of perhaps two, or even three, minutes from the results on the

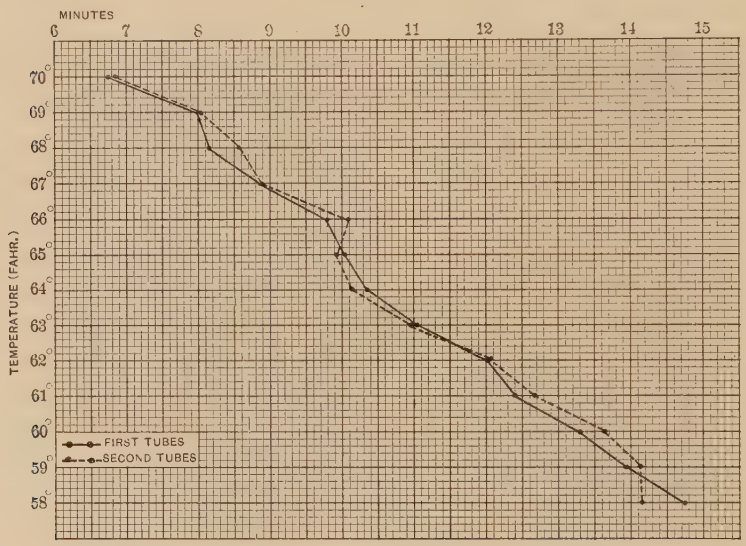

FIG. 2.—The average of the estimations shown in Fig. 1.

previous day. This difference is hard to explain, but undoubtedly exists. It explains how Fig. 1 shows so much variation in results. If, however, the test be done two or three times in rapid succession (which altogether takes less than half an hour, when working at 20° C.), the coagulation time of the individual for that special occasion may be very accurately gauged. Moreover, in diseased conditions, very great variations occur, Sabrazés finding that, with a normal of about nine minutes, cases of acute infection, such as appendicitis, would give readings of two minutes, and hemophilia as high as over twenty minutes. So far, we have confined our observations to the apparently normal.

The age of the individual seems to make little or no difference in the time of coagulation. At 20° C. the average time of children under twelve examined was 8.04 minutes, and of adults 7.72 minutes. Sex has no evident effect, the average time of females examined being 7.54, and of males 7.76.

There has been much difference of opinion as to the presence or absence of a diurnal variation in the coagulation time of the blood; some, such as Bürker,[5] Coleman,[6] and McGowan,[4] believing that such a variation exists, although they do not agree on its time of occurrence. Thus, Coleman believed that coagulation is most rapid in the morning, while Bürker and McGowan came to the opposite conclusion. Others, such as Addis, think that there is no distinct diurnal variation, and with this conclusion our results would on the whole agree, although both in Addis' chart (Fig. 3) and in ours there does seem to be a slight retardation about two hours

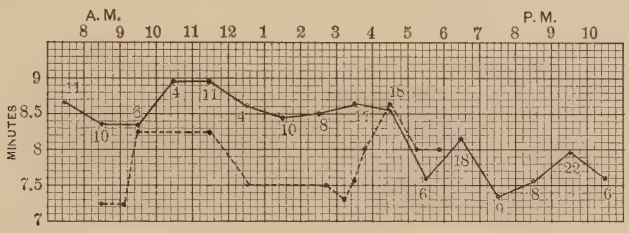

FIG. 3.—The solid line represents the average times of coagulation. All were done at 68° F. (20° C.); the broken line represents Dr. Addis' results, done at 18.5° C., using smaller tubes. The numbers denote the number of separate estimations from which the averages are compiled.

after a meal. Addis thinks that such is within experimental error, but it comes out in ours also at about the same time (Fig. 3).

Generally speaking, a room will probably be cooler in the morning than it will be later in the day, and in any conclusions drawn from experiments where the temperature of the tubes has not been accurately maintained at the same level (as in McGowan's), the conclusion would tend to be that the coagulation time was slower in the morning. Moreover, even when the tubes are kept in a thermostat, a cool room, as already explained, tends to slightly slow the readings. Fig. 3 shows a slight hastening of coagulation toward evening, which is probably accounted for in this way.

The relation to meals has again been much discussed, but our results give no very definite effect of food, except it be the slight slowing of coagulation about two hours after meals already referred to. One would almost certainly expect that certain articles of diet would have an effect upon the coagulation time, but into this point we have not gone.

The temperature of normal individuals, as taken by ordinary clinical methods, varies between 97° and 99° F.,[11] and this must make a difference in the coagulation time, but into this point we have so far not entered. If the finger punctured be cold the blood will be cooler than if the finger be warm.

The effect of the administration of calcium salts upon the coagulation time of *healthy* people appears, from our experience, to be slight, or absent. It was tried several times with each of three healthy individuals, and the average results were as follows:

Male adult, aged forty-four years. Average coagulation time (59 estimations) was 8.27 minutes, at 20° C. Was given doses of calcium lactate, varying from 20 to 60 grains, and the average coagulation time of 14 estimations, made at intervals of one to several hours after the administration of the drug, was 8.56 minutes.

Female, aged twelve years. Average coagulation (13 estimations) was 8.19 minutes. Was given calcium lactate on several occasions, in doses of 10 to 30 grains, and the average coagulation time (of 12 estimations) made within a few hours afterward) was 8.02 minutes.

Male, aged eight years. Average coagulation time (16 estimations) was 7.9 minutes. After various doses of calcium lactate of 10 to 20 grains, it was 7.87 minutes (16 estimations).

Thus, the coagulation time remained practically unaltered through all these tests.

Citric acid was tried in the same way and with results that would suggest a slight retarding action on the coagulation time of healthy persons.

The same three people were tested, and the averages were as follows:

Male adult. Coagulation time before sodium citrate, 8.27 minutes; coagulation time after sodium citrate, 9.44 minutes. The drug was given in 60 grain doses.

Female, aged twelve years. Coagulation time before sodium citrate, 8.19 minutes; coagulation time after sodium citrate, 8.75 minutes.

Male, aged eight years. Coagulation time before sodium citrate, 7.9 minutes; coagulation time after sodium citrate, 7.54 minutes.

The last case showed no retarding effect, but in the other two it was decided. The doses used in the cases of the last two were 30 and 15 grains, respectively, repeated.

Conclusions. 1. The chief object of this communication is to advocate and describe a method of measuring the coagulation time of the blood, which is convenient clinically and which seems to give reliable results.

2. The temperature at which the experiment is carried out makes a marked difference in the results. This difference is about one minute for each degree Centigrade. At 20° C., the average coagulation time is about eight and one-half minutes.

3. Age (beyond early childhood) and sex seem to have no influence upon the coagulation time.

4. A diurnal variation does not seem to occur; possibly there is a slight increase in coagulability as the day advances, but this is probably due to experimental error.

5. There appears to be a slight tendency to decrease in the coagulability some two hours after a meal, but it is too slight to put much weight upon.

6. Calcium lactate does not appear to have any influence upon the coagulation time of the blood of normal individuals.

7. Citric acid appears to have a slight retarding influence upon the coagulation time.

8. Considerable variation occurs in the coagulation time of a healthy individual from time to time, the nature of which is not evident.

I wish to express my gratitude to my colleague, Professor T. G. Brodie, for much valuable advice and assistance, both as regards the work and in the preparing of the charts.

Note.—Since communicating the above my attention has been drawn to two papers by K. Kottman[12] upon the measurement of

the coagulation time of the blood. He uses a Thermos bottle as a thermostat, and describes two methods. One is that of Vierordt, published in 1878, with the addition of the Thermos bottle to regulate the temperature. The other is a new and elaborate one in which the Thermos bottle is again used with the same object.

Messrs. Eimer & Amend, 205 to 211 Third Avenue, New York, can supply the various articles required for the above work.

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EXPERIMENTS AND CLINICAL OBSERVATIONS ON THE EFFECTS OF IPECAC ON AMEBÆ.

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Among the many drugs recommended for the treatment of amœbic dysentery, none have given in our hands as successful results as ipecac. The use of this drug has been followed in every instance by a disappearance of the amebæ from the stool; the rapidity of their disappearance dependent upon the severity of the disease, its duration, and the vigorousness of the ipecac treatment.

The following brief histories of selected cases may serve as an illustration:

Case I.—C. G. P., white, male, aged fifty-two years, schoolteacher. Admitted January 24, 1910.

Present Illness. Patient has always lived in Louisiana. About fourteen months ago (November, 1908) he first began to suffer with diarrhœa. Stools contained at times blood and mucus, and were accompanied with tenesmus; number of stools averaged ten or twelve a day. The diarrhea has persisted, with occasional intermissions, up to admission.

Physical Examination. Negative, except for slight emaciation and slight anemia.

Previous Treatment. Not definitely known, but no ipecac used.

Ipecac Treatment. January 25; examination of stool showed many active amebæ, blood, mucus and pus. Ipecac, gr. xxxv, given at night, and dose reduced 5 grains daily. January 26, amebæ present, but non-motile; some encysted. January 28, no amebæ found in stool. February 1, ipecac course ended; stools show many active amebæ. February 2, all medication by mouth

stopped; patient given quinine bimuriate irrigation, 1 to 1000, twice daily, for next ten days. February 11, amebæ still present; irrigations discontinued. Second course of ipecac begun with gr. xxxv, diminished 5 grains daily. February 14, no amebæ found in stool or by rectal tube. From this time on feces were negative for amebæ, and improved daily. Duration of ipecac treatment in this case was fourteen days. Total amount of ipecac taken, 280 grains (140 grains to each course).

Result. Patient discharged March 12, having gained in weight and strength. Stools normal.

Case II.—A. P., white, male, aged twenty years; occupation, city drummer. Admitted March 7, 1909.

Previous Ailment. Negative.

Present Illness. About eight months ago he suffered with abdominal pains and constipation, alternating with diarrheal attacks. For past three months diarrhea has become more marked—six to eight stools daily—often containing blood and attended with tenesmus. Patient says he has lost weight and strength.

Physical Examination. Patient fairly well nourished; otherwise negative.

Previous Treatment. Consisted mainly of paregoric and bismuth. No ipecac used.

Ipecac Treatment. Amebæ found in stool on March 10. Patient kept in bed, on liquid diet. Ipecac course begun, with gr. xl. March 14, specimen of feces by rectal tube showed no blood or amebæ. From this time on no amebæ were found again, though examinations were made every two days. On the 19th stool was practically normal. Ipecac in this case was administered somewhat irregularly, and occasionally a day or two omitted, but dose was gradually reduced to gr. v. Duration of the ipecac treatment, sixteen days. Total amount of ipecac, 245 grains.

Result. Patient discharged March 29, apparently cured.

Case III.—G. G., white, male, aged forty-five years; occupation, mason. Admitted March 4, 1910.

Present Illness. Began to suffer with loose bowels in September, 1909; was living in Central America (San Jose) at the time. Stools were frequent, very "slimy," and often bloody. He improved under

treatment, but was never entirely free from pain in his abdomen. Another attack of diarrhea began in December, similar to the first, lasting thirty-seven days. After this, bowels were slightly loose, but he felt much better, except for abdominal discomfort, which persisted. Last attack began early part of February, and was of the same character as the former ones, except tenesmus was more marked.

Physical Examination. Patient poorly nourished and anemic. Examination of stool revealed many motile amebæ, mucus, blood, and pus.

Previous Treatment. Consisted chiefly, so far as we could learn, of opiates and colonic irrigations. No ipecac used.

Ipecac Treatment. Amebæ were discovered on March 7, and patient put upon a course of ipecac, beginning with gr. xl, and diminishing gr. v daily. After third day, amebæ could not be found, but reappeared (March 18) eight days later. A second course of ipecac was immediately instituted, commencing with gr. xl, and administered as follows: gr. xl, gr. xxxv, then gr. xxx for next seven days, and discontinued. On third day of second course, motile amebæ still present in stool; two days later no amebæ or blood discovered with rectal tube (March 23). From this time on, bowels rapidly improved. In this case the ipecac treatment lasted twenty-three days. Patient took 240 grains in first course, and 275 grains in second course. Total amount of ipecac, 515 grains.

Result. Patient discharged, apparently well. Has gained twelve pounds in weight. Entirely free from abdominal pain for first time since beginning of illness.

Case IV.—A. B., white, male, aged thirty-six years; occupation, merchant; home, Morgan City, La. Admitted March 30, 1910.

Present Illness. Began about two years ago, with diarrhea—seven or eight stools a day—containing bloody mucus, and accompanied with tenesmus. Bowels have improved occasionally, only to be followed by a similar attack.

Physical Examination. Patient poorly nourished. Has lost about thirty pounds; weak and slightly anemic.

Examination of feces by rectal tube showed many amebæ, mucus, blood, and leukocytes.

Previous Treatment. Medication by mouth, ingredients unknown; no ipecac.

Present Treatment. Given ipecac, gr. xlv, on April 5, and dose reduced 5 grains daily. No amebæ or blood found after fifth day of treatment. Duration of ipecac medication in this case, ten days. Total amount of ipecac, 225 grains.

Result. Patient discharged April 20, much improved.

CASE V.—T. L., white, male, aged twenty-one years; occupation, merchant; home, New Orleans. Seen April 14, 1910.

Present Illness. Began about a week ago, with loose bowels; diarrhea rapidly became more severe, patient having twenty to twenty-four stools in twenty-four hours, accompanied by tenesmus. Passages were small and contained bloody mucus.

Physical Examination. Negative. Stool consisted almost entirely of bloody mucus and pus. No amebæ seen.

Previous Treatment. Consisted of a purge at first, then bismuth, and paregoric by mouth, and 2 per cent. tannic acid irrigations.

Ipecac Treatment. On April 18, specimen obtained by rectal tube showed many motile amebæ. Ipecac given as follows: gr. lx, lv, lxv, xxv, xlv, xlv, xlv, then stopped. On second day of treatment a few encysted forms noted in stool; subsequent examinations of feces negative. Bowels slightly constipated. Duration of ipecac medication, seven days. Total amount of ipecac given, 300 grains.

Result. Patient discharged on April 27, apparently well.

CASE VI.—T. J., white, male, aged seventeen years; laborer. Admitted August 27, 1909.

Present Illness. Has existed for about three weeks; began with loose bowels, about ten in twenty-four hours, containing bloody mucus.

Physical Examination. Patient somewhat emaciated; otherwise negative. Urine and blood examination negative.

Previous Treatment. Patient was treated with irrigations of quinine bimuriate, 1 to 4000 up to 1 to 2000 t.i.d., for twenty-eight days. At the end of this time amebæ still present in stool.

Ipecac Treatment. Irrigations discontinued; ipecac administered as follows: gr. lx, for ten days; gr. xx, for twenty-nine days; gr. x, for twenty-two days. Amebæ disappeared after third day of ipecac

treatment. Total amount, 1400 grains, and duration of ipecac treatment, sixty-one days.

Result. Patient discharged February 9; bowels apparently normal; has gained in strength and ten pounds in weight. Patient was kept under observation for six weeks previous to his discharge.

CASE VII.—T. Mc., white, male, aged fifty-eight years; occupation, sheriff; home, New Orleans. Admitted January 7, 1910. Case was followed through courtesy of Dr. Simon.

Previous History. Thirteen years ago had an attack of obstinate diarrhea. Was treated in Charity Hospital for six weeks, and left much improved. No ipecac was given. Six years ago was treated for a month at Touro Infirmary for diarrhea. No ipecac administered. In July, 1909, returned to Charity Hospital with same complaint. Bowels acted ten or twelve times per day. Stools contained bloody mucus and amebæ; tenesmus present. He received one course of ipecac, beginning with 50 grains, and quinine irrigations. Patient left hospital on September 1, but continued to take 10 grains of ipecac every night for almost four months. Bowels still loose at times.

Present Illness. Began about December 1, 1909, with six to nine actions a day, accompanied with tenesmus, and containing bloody mucus.

Physical Examination. Patient emaciated and weak; otherwise nothing of note.

Ipecac Treatment. On January 19 many motile amebæ found in stool. Course of ipecac begun with gr. xlv, and administered as follows: gr. xl, xxxv, xxx, xxv, xx, xv, x, v, v, x, xv, then gr. x daily until February 9. No amebæ found after third day of ipecac medication, but reappeared February 9, when a second course was at once begun, commencing with 35 grains, and reduced 5 grains daily. A saline enema was given for four days. On February 13 the dose of ipecac was 15 grains. From this time patient was kept on 20 grains of ipecac. On February 15 and 19 amebæ still present in stools. February 23, patient went to Touro Infirmary. Received ipecac, gr. c; next day, lxxx; next, lx; then l. After this, dose reduced 5 grains daily. No amebæ found after third day. Proctoscopic examination made by Dr. Simon and Prof. Dock, after

admission to Touro, revealed many large, deep, and irregular ulcers. Another examination two weeks later showed ulcers almost completely healed. Between first and second examinations patient had had silver nitrate irrigations, 1 to 5000 down to 1 to 1000 strength, twice a day. March 26, patient sitting up, still on 10 grains of ipecac daily. Bowels almost normal. March 31, discharged.

Result. Patient left, apparently well so far as his dysentery was concerned, though still somewhat weak. One week after being discharged, patient overexerted himself, had an acute dilatation of the heart, and died in a few days. No autopsy permitted. His case demonstrates the futility of small doses of ipecac in long-standing cases. Duration of ipecac treatment, seventy-two days. Total amount of ipecac, 1385 grains.

The cases cited above suffice to show the effect of ipecac upon the amebæ. Many more cases were treated with ipecac, but for various reasons were not considered available for this paper. In some instances other parasites were found in stools in conjunction with the amebæ, as strongyloides, uncinaria, trichocephalus; so that the disease could not be looked upon as amebic dysentery pure and simple. In other instances ipecac was used in connection with other therapeutic measures, as colonic irrigations of quinine, tannic acid, saline solution, creolin, etc.; or, again, additional medication by mouth, making the result difficult to interpret as to whether the good effect was due to ipecac, *per se*, or other drugs employed. In every case patients were put on liquid diet and kept in bed until the amebæ disappeared and stools showed marked improvement.

Dose of Ipecac. As the proper dosage of ipecac is not definitely known, it was decided, at first, to try small amounts, in order to determine the lowest efficient dose. Treatment was begun on 35 grains, and reduced 5 grains daily. In a number of cases this dose was found to be too small, especially if reduced 5 grains daily, and a second course of the drug became necessary, thus prolonging the treatment. Cases I, III, and VII illustrate this point, though occasionally this method may be successful, as shown in Case IV. Experience has demonstrated to us that far better results are obtained by giving 50 to 100 grains of ipecac a day, and the dose continued until the amebæ disappear and the diarrheal symptoms improve.

A short, vigorous treatment will often accomplish in a few days what a mild one fails to do over a long period of time. One of our cases prior to admission to hospital took 10 grains of ipecac for almost four months, yet was not cured.

Administration of Ipecac. Ipecac is best prescribed in salol-coated pills. Such a pill, containing 5 grains of ipecac, is usually as large as can be comfortably taken by the average patient. It is important that the pills should be carefully prepared, for if insufficiently coated, they will cause vomiting. On the other hand, if the coating is excessive, some of the pills may be passed in the stools practically intact. This occurred once each in three of our cases. The question arises as to whether the salol in the ipecac pills may not be a responsible factor in the good effect noted in amebæ cases. We have never been able to discern any beneficial effect from its use alone. The amount of salol in a machine-made pill is about 2 grains. Pills made by hand contain 2 to 4.5 grains of salol.

The giving of opium in some form previous to the administration of ipecac is sometimes advised. None of our patients received any opium, except one by mistake. In this case 15 minims of tr. opii were taken one-half hour before the ipecac, "to prevent vomiting." This is almost always an unnecessary precaution, as there is no advantage in opium unless especially indicated, and no vomiting will occur, providing pills are properly made. In Case V, patient was given 60 grains of ipecac as an initial dose, which caused him to vomit for several hours. On examining the pills, it was found that they were insufficiently coated, and had been put up by an inexperienced druggist. Upon repeating the dose the following day with properly made pills, the patient had no difficulty whatever in retaining them.

The ipecac pills are best taken at night, and all nourishment should be discontinued during their administration.

Local Measures. Irrigations of the bowels with various agents, as quinine, tannic acid, silver salt, and other solutions, have their sphere of usefulness; this is especially true where ulcers exist and can be reached, in which case the irrigating fluids probably destroy any amebæ they come in contact with, particularly if non-encysted. It is exceedingly doubtful, however, whether the irrigations ever

reach all the amebæ in the gut. In two of the above cases quinine irrigations were employed alone. Case VI was irrigated t.i.d. for twenty-eight days with quinine bimuriate solution, from 1 to 4000 to 1 to 2000 strength. At the end of this period amebæ were still present in the stool. Case I had irrigations with quinine bimuriate solution, 1000, twice daily for ten days, with same result. This experience has occurred in other cases and with other antiseptics, including tannic acid. In our opinion, irrigations are to be looked upon as accessories to the ipecac treatment.

Supposed Ill Effects from Ipecac. Thus far we have seen no bad effects from the use of ipecac. In Case VI the ipecac was taken for sixty-one days, total amount being 1400 grains, yet patient showed no ill effects from the drug. One patient took 300 grains in three days without any apparent discomfort. He vomited once the first day, due to the fact that he was given some nourishment by mistake while taking the pills. Patients rarely show any signs of depression; on the contrary, the improvement of the dysenteric symptoms usually causes them to feel much better. Occasionally the drug may cause the diarrhea to persist, with considerable bile in the stool, in which case the ipecac should be discontinued and the stools watched for a few days. They will rapidly become normal if the amebæ have been destroyed and ulcers do not exist.

Blood Pressure. We examined the blood pressure in order to see whether the supposed depressant action of ipecac would show in the circulation. Case W. A., prior to the administration of ipecac, had a blood pressure of 90. He was given 100 grains of ipecac at night, and the following morning (March 26) blood pressure was 105. On the 27th, after another 100 grains, blood pressure was between 100 and 105. On the morning of the 28th, after still another 100 grains of ipecac, blood pressure was between 115 and 120. March 30, blood pressure, 105; no ipecac for two days.

Case S. D., January 29, blood pressure was 122 and 127. On January 6, blood pressure, 116 to 110; no ipecac given. January 8, patient at 8.45, blood pressure, 93 to 95. No vomiting. At 8.55, ipecac, gr. 40; at 9.05 blood pressure was 105; at 9.10 blood pressure was 105; at 9.30 blood pressure was 102 to 103; at 10 blood pressure was 111; at 10.20 blood pressure was 107; at 11 blood

pressure was 103. On January 9, at 8.30 A.M., blood pressure was 120.

It would then seem, contrary to what we would expect, that the blood pressure is not lowered by ipecac, even in very large doses.

Examination of Stools. The ipecac treatment was controlled by numerous microscopic examinations of the stool. Only fresh stools were examined or specimens of feces obtained by rectal tube. In almost every case we failed to observe active amebæ after three days of ipecac medication, though not infrequently non-motile amebæ and encysted forms were noted. In all our cases where active amebæ reappeared in stools the patients were taking but 5 or 10 grains of ipecac, or had finished the first course. The amebæ observed in every case corresponded to Schaudinn's Entamœba histolytica. Stools on first examination showed mucus and blood, some of them pus and sloughs. After the disappearance of the amebæ, blood could seldom be detected. Mucus was the last element to disappear from stools. It is advisable not to rely entirely upon the fresh stool when searching for amebæ, for the stool may show no amebæ or blood when the specimen obtained by rectal tube will reveal both. This is easily explainable from the pathology of the disease; the amebæ being embedded in the wall of the gut or ulcers, and thus protected from being swept out by the stool. The rectal tube, however, scrapes the amebæ from the mucosa.

Stool Cultures. From the feces of almost all the cases in which amebæ were found, cultures were made upon plates of Musgrave and Clegg's medium, before and after treatment with ipecac, in hopes of gaining some information in regard to the value of cultures as a diagnostic method and control of treatment. The cultures, however, were disappointing. We failed in two of the above cases to get any growth of amebæ. In the remaining five cases no growth was obtained in three cases before treatment was begun, though the medium was inoculated with bloody mucus containing amebæ in large numbers. After treatment had been instituted they were often isolated in culture when for many days they could not be found in the feces.

Brief Description of Types of Amebæ Observed in Cultures. A very small ameba was frequently met with in culture which corre-

sponds somewhat to the limax. It never appeared larger than 20 mikra, was granular throughout, with no clear differentiation between ectosarc and endosarc. Unstained, no nucleus was visible, though it contained a slowly contractile vacuole. Its cysts were small, dark, oblong bodies. This small type of amebæ we have since obtained from the stools of the two non-amebic cases. Besides this apparently harmless variety, two other forms were isolated, very similar in appearance to each other, but differing as regards their cysts—one having an irregular stellate cyst, the other, round. These two types were quite large, varying in size between 30 and 50 mikra. They showed a clear differentiation between endosarc and ectosarc, containing a large contractile vacuole, a nucleus, and nucleolus. The encysted forms of these two types have been fed to kittens, without any result thus far.

Our work of the past year leads us to agree with the extensive observations of Dr. Couret, that the amebæ which have been cultivated are probably not the histolytica.

Proctoscopic Examinations. It is claimed by some that amebæ can be found in curettings of ulcer, even if none can be demonstrated in stools or by rectal tube. We have examined several cases of severe amebic dysentery per proctoscope without finding any ulceration whatever in rectum, or as high as proctoscope reached, about eight inches.

EXPERIMENTS.

These experiments were undertaken with a view to finding out, if possible, the manner in which ipecac acts. For this purpose we decided to employ amebic cultures, as they could be most easily handled and controlled. Such experiments have been performed upon cultures of amebæ with numerous antiseptics by Thomas,[1] but no tests have been conducted, so far as we are aware, to determine the action of ipecac. We have no idea of detailing our work with cultures, as they have but a negative value. It is quite possible that the cultivatable forms of amebæ may be more

[1] Action of Various Chemical Substances upon Cultures of Amebæ, J. B. Thomas, Bureau of Government Laboratories, No. 23, June, 1905.

resistant to ipecac than the histolytica. A few experiments were tried at first upon living amebæ in dysenteric stools, but the results were unsatisfactory, owing to the fact that patients could not be kept without treatment and that the amebæ lost much of their motility in transportation in cold weather from hospital to laboratory.

Amebic Cultures. Two cultures of amebæ were used for the experiments, one of which was obtained from Dr. Couret, and the other selected from one of our cases. Both cultures were isolated from dysenteric stools and grown upon Musgrave and Clegg's[1] special agar medium, in symbiosis with colon bacilli.

Preparation of Ipecac. Ipecac suspensions were made by mixing powdered ipecac and sterile distilled water in various dilutions. These water suspensions were frequently shaken and only used after an interval of at least four hours.

Experiments. *Method I.* In our first experiments the ipecac was incorporated in the special agar medium. One c.c. of varying concentrations of a watery ipecac suspension was added to tubes containing 9 c.c. of the previously liquefied special medium, poured into Petri dishes, and allowed to harden. The medium contained ipecac in dilutions from 1 to 1000 to 1 to 100. Controls were made by adding same quantity of sterile water to the medium instead of ipecac suspension. Forty-eight-hour cultures of amebæ were then transplanted with their symbiotics to these ipecac plates, kept at room temperature, and examined at intervals of two, four, and six days. The amœbæ grew moderately well, as compared with the controls upon all the ipecac plates except in the 1 to 100 concentration; here it was difficult to interpret the result, as the medium was rendered so opaque by the ipecac that the amebæ could scarcely be recognized when present. The results, as a whole, after many experiments with this method, were negative.

Method II. It was thought advisable, in the following experiments, to use one strain of amebæ only, in order to obtain a greater uniformity of results, and, owing to the fact that Dr. Couret's amebæ was the hardier of the two, it was selected. In these tests we followed the technique employed by Thomas, with slight modifications. The medium was not altered, but the amebæ were subjected to the action

[1] Bulletin No. 18, Biological Laboratory of the Government Laboratories, October, 1904.

of ipecac suspensions. Amebæ were grown on slants of the special medium for forty-eight hours, and ipecac suspensions of 1 to 100 to 1 to 10 strengths added to slants and allowed to remain in contact with the amebæ for ten minutes to an hour, poured off, and surface of slants gently washed with sterile water to remove traces of ipecac, and then making transplants from surface to fresh media. Control transplants were made from every amebæ slant previous to adding watery suspension of ipecac. The results of this method showed that ipecac had some influence in inhibiting the growth of the amebæ in 1 to 20 concentration for twenty minutes or over. The symbiotics were but slightly affected.

Method III. Thomas suggested the possibility of many of the amebæ in slant growths being protected by those above them, thus escaping the action of the solution. In the next experiments we followed in general the technique which he employed. From forty-eight-hour slant cultures of amebæ transplants were made to fresh medium as controls (Control I); then to each slant was added 4 c.c. of sterile water and the surface of the slant carefully scraped off into the fluid with a platinum loop. The resultant suspension was poured into sterile test-tubes. From each of these tubes 2 c.c. of amebæ suspension were removed and added to equal amounts of sterile water for varying lengths of time as an additional control (Control II). To the remaining 2 c.c. of amebic suspension, 2 c.c. of a watery ipecac suspension were added for periods of twenty to sixty minutes in concentration of 1 to 20 to 1 to 80. After the desired length of time, transfers of two loops made were from all tubes (including Control II) to Petri dishes containing the special medium, the amebæ allowed to develop for two days, when plates were carefully examined. The table given below represents the results obtained by this method.

Dilution of watery ipecac suspension.	Ipecac susp. applied minutes.	Growth of Amebæ after exposure to ipecac susp.	Growth of symbiotic bacterial.	Control I.	Control II.
1 to 20 . . .	30	Very slight.	Yes.	Fair.	Fair.
1 to 40 . . .	20	Very slight.	Yes.	Good.	Slight.
1 to 60 . . .	40	Very slight.	Yes.	Good.	Slight.
1 to 40 . . .	60	Very slight.	Yes.	Good.	Fair.
1 to 80 . . .	40	Very slight.	Yes.	Good.	Fair.
1 to 80 . . .	60	Slight.	Yes.	Good.	Fair.

In doubly controlling these experiments, we obtained a fairer idea of the relative growths of amebæ treated and untreated with ipecac. In Control I, where the amebæ were transferred directly from the forty-eight-hour slant culture to the plates, practically all showed good growths. In Control II, however, the amebæ were in the same dilution as those treated with the ipecac suspensions, and consequently the growths are less than in Control I, though somewhat greater in each instance when compared to the amebæ exposed to the action of the ipecac. Thomas, in his tests, only made use of Control I. From this table and other experiments along this line we were able to note but a slight inhibitive action of the ipecac upon the amebæ.

Method IV. Stool extracts. In order to determine, if possible, whether the apparent good effect of ipecac in amebic dysentery was due to the fact that the drug underwent some change in the body, which increased its deleterious action upon the amebæ, we undertook the following experiments:

Stools were collected from patients receiving ipecac, in which no amebæ had been found for at least two or three days, filtered, and the filtrate autoclaved. The sterile fecal filtrates were utilized instead of watery ipecac suspensions, according to the last two methods described. The filtrates were not diluted, and were allowed to remain in contact with the amebæ from one to sixty minutes. The results of these experiments showed a very slight diminution in the growth of the amebæ which had been treated with the filtrate for fifty or sixty minutes, as compared with the controls.

Summary of Results of Experiments. From our experimental work we are, at the present time, unable to explain the clinical effect of ipecac in amebic dysentery. In a few of our experiments ipecac apparently possessed some slight inhibitive power on the amebæ, but the results were not sufficiently marked to warrant any definite conclusion. The fact that it is highly probable that amebæ grown on artificial media are not the Entamœba histolytica may possibly account for our lack of success. At all events, we offer the work simply for its negative value.

OBSERVATIONS ON INTESTINAL INFANTILISM.

By CHRISTIAN A. HERTER, M.D.,
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I DESIRE here to call attention to a form of intestinal disorder associated with arrest of development which has as yet hardly received the attention which it deserves. For more than twelve years I have been aware of the existence of the type of disease to which I refer, but it is only recently that I have had an opportunity to work carefully at the pathological conditions involved. So far as I am aware, the condition of intestinal infantilism had not been recognized as a pathological entity by English or American investigators previous to my publication[1] (1908). In Germany, however, a condition of disease in children has apparently been clearly recognized for many years by Professor Heubner,[2] of Berlin, although he did not publish on the subject until about the time of my own publication. It seems probable, also, that some of the cases imperfectly described by Schütz[3] are of the same nature as those described by me under the name of intestinal infantilism and by Heubner under the name of severe intestinal insufficiency in children above the age of nurslings.

It is not my intention to enter into anything like a full description of intestinal infantilism in this place, but rather to briefly state the leading characteristics of the disease, which stamp it as a definite pathological entity, and furthermore to discuss some special features

[1] On Infantilism from Chronic Intestinal Infection, The Macmillan Co., 1908. Translated also into German by Dr. Ludwig Schweiger, Franz Deuticke, Leipzig u. Wien, 1909.

[2] Ueber schwere Verdauungsinsuffizienz beim Kinde jenseits des Säuglingsalters, Jahrb. f. Kinderheilk., 1909, lxx, 667.

[3] Chronische Magendarm-Dyspepsie im Kindesalter, Jahrb. f. Kinderheilkunde, 1905, lx, 794.

about which there exists a difference of opinion between Professor Heubner and myself.

The condition of intestinal infantilism has its beginning usually in the second, third, or fourth year of life, and may have its onset in acute or subacute catarrh of the intestine and an enterocolitis; or it may perhaps develop insidiously and without definite warning. It is doubtless correct to regard the disease in its fully developed form as a rare one, although it must be true that in a large country, like the United States, a considerable number—probably many hundreds—of instances exist. Without making any special effort to bring to light a large number of these cases, I have now observed 10 of them, and I know of a number of other instances in the practice of my colleagues which are almost certainly of the same nature as those which I have studied. The circumstance that the disease is nearly always seen among the children of well-to-do persons is probably to be explained, as suggested by Professor Heubner, on the supposition that the less well-protected children of the poorer classes do not long survive, if they develop this disease.

In every case that has come under my observation there has been a history of periods of disturbed nutrition with loss of weight alternating with periods of improvement in nutrition and gain in weight. These variations ended in each case in a state in which there was apparently a complete arrest of the developmental processes. Although the most obtrusive signs of digestive disturbance, such as diarrhea and flatulence, were in many instances measurably controlled by suitable treatment, there yet remained an arrest of growth, and the utmost difficulty was experienced in bringing about any noteworthy increase in weight and improvement in nutrition.

I have divided the clinical characteristics of intestinal infantilism into two groups—a major and a minor. In the group of major or essential clinical features are (1) arrest in the development of the body; (2) various obtrusive disturbances referable to the intestinal tract, especially large, characteristic fatty stools; (3) marked abdominal distention, due to dilatation of the colon and the accumulation of gas; (4) the rapid onset of physical and mental fatigue, the former being associated with flaccidity of the muscles; (5) the development of a moderate grade of anemia; (6) the maintenance

of a good grade of mental power and fair physical development of the brain, as indicated by the size and shape of the skull. As examples of the physical arrest of development I may instance one of my patients who at seven years weighed only twenty-five pounds and had a height of only thirty-six inches, and also another case in which the patient—a boy—though sixteen years of age, weighed only forty-four pounds and had a height of only forty-three inches. The character of the intestinal disturbance varies somewhat in different instances, but the occurrence of abundant soft stools containing an excess of neutral fat and an abundance of soaps of calcium and magnesium is characteristic. The movements are not, however, always of this character in the same case, but show considerable variation, with, however, a strong tendency for the characteristics just described to recur at short intervals. The excess of fat is often sufficiently great to constitute a condition of true steatorrhea, if thereby we imply a loss of fat serious to nutrition. Pronounced watery diarrheal attacks occur in some instances, but I think they may be said to be comparatively rare. In one of my cases there was no history whatever of diarrhea in the ordinary sense, although the voluminous gas- and fat-holding stools were a feature which existed in alternation with constipation and apparently nearly normal movements. During the time when the characteristic voluminous stools are obtrusive the patients are in especially poor condition and show a loss of weight, together with disturbances in peripheral circulation, which are shown by cold hands and feet and a pinched and sometimes cyanotic appearance in the face. These disorders, though often of short duration, may cause a good deal of prostration, and in severe cases the patients are so much enfeebled as to get about only with greatly increased difficulty. When the diarrhea ceases there is a tendency to rapid recovery, although a loss in weight of half a pound or a pound suffered during a few days of pronounced digestive disturbance may not be regained for several weeks.

Among the minor or accessory clinical features which have been observed by me in intestinal infantilism are to be included slight indications of rickets, excessive sweating about the head during sleep, irregularities of appetite, which is sometimes excessive, in-

creased thirst, increased volume of urine, and various signs of nervous instability. A subnormal temperature with cold and pale hands and feet may commonly be observed. The skin is apt to be dry and rough, but this latter manifestation is one that is corrigible by means of suitable bathing and rubbing. The tongue is apt to be somewhat more red than normal and the papillæ swollen, but there is no tendency to the development of "geographical tongue." The entire tongue may be slightly swollen and may present indentations from the teeth.

Considerable time has been devoted to the study of the bacterial flora of the intestine in cases of infantilism of the type under consideration. As a result of these studies it becomes evident that it is necessary to distinguish between the conditions present during what one may call the active stage of the disease and those present in the later stages. Under the latter conditions where the abnormal processes have lasted for a period of time—say eight or ten years—the bacterial conditions may show nothing characteristic or definitely pathological, despite the fact that there exists a great arrest of development. On the other hand, if we study our patients during the active period in which the characteristic disturbances of digestion occur, we can count on meeting types of bacterial flora which, so far as I am aware, we do not meet in the same numbers and combinations either in normal conditions or in other disorders of digestion. The methods of study which have proved most serviceable in this investigation have been the study of Gram-stained fecal fields; second, the study of the sediments of the saccharose, lactose, and dextrose bouillon and plain bouillon fermentation tubes after inoculation with the mixed fecal flora; and third, a variety of aërobic and anaërobic cultural procedures involving the use of many kinds of media made necessary by the difficulty of growing certain species of bacteria on ordinary media. A striking feature in well-marked cases is the preponderance of Gram-positive microörganisms. Study showed that the organisms in question corresponded to the *B. bifidus* of Tissier, the *B. acidophilus* of Moro, and a hitherto apparently undescribed organism which we have called *B. infantilis.* It is not my intention here to enter into a detailed description of the flora found in cases of intestinal infantilism. It will suffice to indicate certain special points which it seems desirable to emphasize.

The presence of *B. bifidus* in the intestinal contents of our cases of infantilism is indicated in part by a study of the sediments of the sugar bouillon fermentation tubes. The inoculation of the mixed flora into the sugar bouillon fermentation tubes leads commonly to an abundant or more scanty growth of bifid organisms which can be shown to have all the morphological and cultural characteristics of the organism first described by Tissier. It is not possible to state to what extent the intestinal contents may consist of *B. bifidus,* which exists there only seldom in the bifid form and generally in the form of plain rods with narrow or pointed ends. The organism which we have named *B. infantilis* is probably present very abundantly in most or all cases of well-developed intestinal infantilism. It occurs as a Gram-positive rod, agreeing closely in size with the plain form of Tissier's *B. bifidus.* It is not clear that it differs materially from the latter in any morphological characters. The organism has the peculiarity of growing aërobically on suitable media and forming spores. Many cultures have the further peculiarity of forming a pellicle from which may be extracted a mucinous and possibly also a fatty material.

I cannot pass over without comment the strong possibility of a relationship between our *B. infantilis* and an organism very recently studied and described by H. Noguchi[1] as a phase of *B. bifidus.* Noguchi, starting with branching organisms apparently of the bifidus type, succeeded in cultivating an aërobic, spore-forming, pellicle-producing culture which corresponded very closely in details to our *B. infantilis.* By a gradual training of these organisms to anaërobic life, Noguchi was able to bring about a complete reversion of the aërobic phase of this bacillus into an anaërobic phase—results which one would be inclined to regard as almost unbelievable excepting when occurring in the experience of so highly trained and experienced a technician as Dr. Noguchi. These results he obtained by cultivating the bacillus semi-aërobically and then abruptly diminishing the quantity of oxygen after three or four successive cultures. The details of this reversion as described by Dr. Noguchi will well repay study. Not the least interesting conclusion drawn

[1] Pleomorphism and Pleobiosis of Bacillus Bifidus Communis, Jour. Exper. Med., 1910, xii, 182.

by Dr. Noguchi is that *B. bifidus* of Tissier corresponds in its aërobic phase with *B. mesentericus* (fuscus). Noguchi calls attention to the fact that *B. mesentericus* is one of the most widespread saprophytes, and is constantly found on the surface of the skin. He considers the only source of *B. mesentericus*, that is to say, *bifidus*, in the stools of breast-fed infants to be the breast itself.

I am not disposed to doubt the validity of these conclusions of Dr. Noguchi, which may prove of considerable practical importance in the interpretation not only of the flora of intestinal infantilism but of the intestinal tracts of young children in general. Dr. Kendall was inclined to class *B. infantilis* with the subtilis group rather than with *B. mesentericus*, but it is perhaps true that the very slight degree of liquefying power observed in this organism would make it more appropriate to class our organism in the mesentericus group than in the subtilis group. The chief difficulty which I see in an agreement of our results with those of Noguchi is that *B. infantilis* exhibits so few characteristics of ability to induce even slight putrefactive decomposition with formation of indol, hydrogen sulphide, etc. If it should prove to be the case, as seems to be probable, that *B. infantilis* represents simply one phase of *B. bifidus*, and that both these organisms are essentially members of the mesentericus group, it will not merely clear up some puzzling features in the bacteriology of the digestive tract, but will emphasize still more strongly than I have been able to do the great numerical importance of *B. bifidus* in cases of intestinal infantilism. I have suggested that in our cases of infantilism perhaps the most striking feature is the persistence of bacteria characterizing the infantile period of life, into a period extending many years beyond this. The work of Noguchi seems to me to help to substantiate the correctness of this view.

Besides the bacterial features mentioned there are two others which deserve a passing word. First, coccal forms are sometimes very abundant. Their numbers, however, vary a good deal in the same case at different times. They are commonly Gram-positive, and the diplococci and coccal bacilli may correspond closely in morphology and cultural characteristics to the enterococcus of Thiercelin or the *Micrococcus ovalis* described by Hirsch-Libmann. The relation of these organisms to the others in the digestive tract

is not yet clear. The second point which I would mention is that in well-marked cases of infantilism the organisms of the *B. coli* group may be wholly deficient in the stools or present only in very small numbers. This is a peculiarity which is certainly noteworthy in children beyond the infantile period of life. A phase of this peculiarity to which I attach considerable importance is the reappearance of organisms of the *B. coli* type coincident with the gradual recession of organisms of the bifidus and *B. infantilis* types.

In my original publication on infantilism I pointed out that the two leading features, distinct but related, of intestinal infantilism which must be considered in any endeavor to picture the morbid processes on which the clinical manifestations depend are, first, extreme retardation in the general bodily development, and secondly, the state of intoxication which manifests itself in well-marked derangements of the neuromuscular system. As regards the retardation of development, I think I have been able to bring forward sufficient evidence to support the contention that the arrested growth can be explained by the inability of the organism to secure an adequate supply of nutrient material from the contents of the digestive tract. Careful balances indicate that the failure to absorb sufficient calcium and magnesium accounts for the arrest of skeletal growth, while the restricted absorption of carbohydrates and fats explains the failure to store fat, and at least partially accounts for the cessation in the growth of the muscles. The proportionate slowing in the growth of the viscera may safely be assumed to have a similar origin, although possibly here the physiological adaptation of visceral structures to the needs of the rest of the body may have an influence. The relatively large development of the head and brain may be dependent in part on the large size of the brain at birth, but it seems that the growth of the brain in infantilism is distinctly out of proportion to the very slow growth of other parts of the body.

It is seen that the cardinal features of infantilsm, the prolonged arrest of development in infancy and early childhood, may be attributed mainly to an impaired power of absorption of fats, salts, and proteins. Between the absorption of fats and the absorption of the salts of calcium and magnesium there appears to be a close relation-

ship. It has been mentioned that the characteristic stools in infantilism contain considerable quantities of the soaps of calcium and magnesium, and it may well be true that the failure to absorb these soaps is one of the most important elements in that deprivation of mineral constituents which is the basis of the retardation of the skeleton. The relation between insufficient carbohydrates and defective absorption appears to be very remarkable, for the restriction in this class of foodstuffs is one often encouraged by the physician on account of the evil consequences often following even the moderate use of sugars and starches. Very likely the inability of the intestine to completely absorb the dextrose formed during the digestion of starches is a factor in robbing the organism of a proper share of carbohydrates, but to this factor is certainly added the loss occasioned by the excessively rapid decomposition of dextrose by acid and gas-producing bacteria. I have attributed the impaired power of absorbing foodstuffs from the intestinal tract to a chronic inflammatory process involving especially the lower portion of the colon. I have based this view on the occurrence of mucus, epithelial cells, and leucocytes intimately mingled with the intestinal contents. The existence of an inflammatory condition in the intestine is questioned by Heubner, who is disposed to regard the state of the intestine as one of functional insufficiency and atony without definite inflammatory origin. I admit that there are periods in the history of cases of infantilism in which the indications of inflammation are slight and unobtrusive, but I believe that these periods represent times of temporary subsidence of a persistent, chronic inflammation of varying intensity and distribution. Heubner questions the ability of normal intestinal bacteria to bring about intestinal inflammation in older children, and does not consider it clear that the hypothetical inflammation of the intestine could lead to so severe a disturbance as this of infantilism.

I do not pretend to be able to satisfactorily define the role of the disturbed bacterial conditions in the production of infantilism. It is conceivable that the bacterial conditions may be regarded as secondary, wholly accidental, and therefore in no sense causative. There is, however, one very important consideration which should not be overlooked in this connection. This is the fact observed in

many of my cases and admitted by Professor Heubner for several of his cases, that the onset of the state of infantilism is often consecutive to acute or subacute disorders of digestion in which it would appear that bacteria play a very definite part and are the occasion of definite inflammatory conditions. I make no claim that the organisms of the bifidus type, including, perhaps, *B. infantilis,* are definitely pathogenic in the accepted sense of that word, but am strongly inclined to maintain that these organisms have, perhaps in part through their acid-producing properties, acted as mild irritants capable by their persistence and wide extent of initiating disturbances in function. I have also to own that in ascribing to bacterial and to chronic variable and mild inflammatory conditions an important role in the pathology of infantilism, I am influenced by my experience with chronic inflammatory conditions in adults. I believe there exists definite evidence, at present only imperfectly studied, to the effect that chronic ileocolitis associated with a preponderance of abnormal types of bacteria is responsible for many chronic disorders of nutrition characterized by gradual shrinkage of the general bodily tissues, including the muscles and skeleton.

I do not, however, care to pursue this controversial point farther at the present time, and I shall conclude what I have to say about the pathology of intestinal infantilism by reference to the part played by the products of abnormal intestinal decomposition in bringing about certain toxic symptoms which occur in the course of the disease. On this point also Professor Heubner has expressed skepticism. My experience leads me to think that the element of intoxication is very variable in different cases of infantilism, being in some examples of the disease characteristic, extending over years in unmistakable intensity and definiteness, and in other cases being a subordinated or relatively unobtrusive condition at least during a portion of the time. The patient in whom the toxic symptoms are well defined may show these manifestations in a variety of ways. The most prominent of such symptoms are irritability of the nervous system, shown in emotional overaction and heightening of the reflexes. This emotional overaction is apt to alternate with mental and emotional depression. Circulatory disturbances are common, the face being sometimes flushed and the lids swollen and drooping;

more frequently, however, the face is pinched. There is at times a little rise in temperature which apparently can be explained only on the supposition of some kind of intoxication. Most striking of all is the rapid muscle fatigue which sets in after slight exercise. Indeed, in many instances the muscles themselves become thin and flabby.

It appears to me that these conditions can only be regarded as having a toxic origin. Their great variability within relatively short periods of time is an additional confirmation of this view. Moreover, it is precisely in the cases which show these peculiar disturbances of neuromuscular function that we find most strongly marked the evidences of excessive and abnormal intestinal putrefaction. These evidences consist in an increase in the ethereal sulphates, indolacetic acid, aromatic oxyacids, and volatile phenolic substances. It is true that not all these need be present in the same case. I consider the rise in the ethereal sulphates and the excess of aromatic oxyacids the most constant features of excessive putrefaction in the active stage of intestinal infantilism. The presence of considerable indoxyl potassium sulphate is a variable condition —very marked in some cases, much less marked in others, and often highly variable in the same case. In some instances great excess of indolacetic acid is a continuous feature. It shows, as I have already pointed out, as the urorosein of the urine.[1] I am inclined to associate marked muscular prostration with a constantly striking excess of indolacetic acid or with extreme indicanuria in the urine. Particularly noticeable in this connection is the fact that these various nervous symptoms tend markedly to retrogress when there is a recession in the formation and excretion of the substances I have mentioned. Another point which I would emphasize strongly because I think it is too much overlooked by clinicians and pathologists, is the fact that it has been shown that indol in very small quantities is capable of inducing rapid muscle fatigue. I have not had an opportunity to study the influence of indolacetic acid in this relation, but it appears in a high degree probable that

[1] The Relation of Nitrifying Bacteria to the Urorosein of Nencki and Sieber, Jour. Biol. Chem., 1908, iv, 239; also, On Indolacetic Acid as the Chromogen of the "Urorosein" of the Urine, ibid, 1908, iv, 253.

it possesses a similar depressant action on the voluntary muscles. The similarity in chemical constitution to indol gives color to this view. It should be remembered also that while indol undergoes oxidation, and is thus got rid of in the form of the indoxyl compound, indolacetic acid undergoes little or no oxidation in the body, but is excreted as such, thus giving it opportunity to act upon the neuromuscular structures.

For these reasons, which might be considerably elaborated, I maintain that the toxic symptoms observed in many of our cases of intestinal infantilism have their most reasonable explanation in the action exerted by products of decomposition in the intestinal tract. I am not prepared to maintain that fever is caused by any of the substances mentioned, nor can I believe that it is due to inorganic salts, as some investigators claim. It seems more likely to be dependent on substances the nature of which have as yet escaped attention.

As regards the therapeutic modification of the conditions existing in intestinal infantilism, it is almost impossible to make a general statement applicable to all cases. The symptoms of the disease vary so much in different cases, and from day to day in the same case, that it is necessary for the physician to gain his own experience in the application of the therapeutic principles that emerge from a rather complex combination of processes. The environmental requirements in these cases are very well defined. They call for a temperate, equable, and sunny climate, in which the patient can live out of doors; and secondly, they call for quiet and soothing human surroundings and limited companionship. Dietetic measures are, of course, the keystone of the therapeutic situation in this disease. Without the closest attention to them there is small chance of favorably modifying the intestinal processes which underlie the condition. Cautious and prolonged observation and experiment are necessary to secure the best dietetic conditions in each case. The task of the physician is to secure the absorption of foodstuffs adequate in quality and quantity for a moderate growth of skeleton, muscles, etc., with as little waste as possible from non-absorption and as little opportunity as possible for excessive putrefaction. The intelligent restriction of the carbohydrates is an absolutely essential

feature in the management of these cases. Rice appears to be one of the best forms in which carbohydrates may be allowed. Of equal importance is the careful regulation of the fats. The guiding principle here consists of giving only so much fat as will be in large measure absorbed. It is desirable to avoid the prolonged formation of excessively fatty stools. The main objections to such an excessive fat loss are two—the unnecessary and uneconomical waste of calcium and magnesium soaps, and the interference with digestion and absorption occasioned by the presence of fatty material in excess. The proteins are better tolerated than either fats or carbohydrates, but it is necessary to experiment in order to see what form of proteid is best utilized. Some children do badly on eggs, although most of them tolerate egg-white. Beef, mutton, and chicken, or broths made from these, are usually well taken. The necessity for cutting down the carbohydrates and fats in the treatment of infantilism leads to a corresponding tendency to increase the protein above the ordinary proportions in food. This is objectionable in favoring excessive intestinal putrefaction. This undesirable tendency may be in a measure overcome by the free use of gelatin, which is capable of replacing the carbohydrates and fats within moderate limits. The chemical constitution of gelatin is such that it does not give rise to indol, skatol, indolacetic acid or aromatic oxyacids. This fact can be utilized in this connection. I believe I have made use of this form of food in a highly advantageous manner in several of the cases of intestinal infantilism which I have closely studied.

It is difficult to give definite rules in regard to the use of milk. The experience of Heubner is apparently strongly against the use of milk, and the fact that in this disease we seem to be dealing with the persistence of certain modified flora of infancy—flora growing readily in milk—may afford an explanation of the intolerance for milk which exists in many cases. My experience, however, has been that some children are able to tolerate considerable quantities of plain or fermented milk. Therefore, I am not disposed to wholly abandon the use of milk without a careful trial. Buttermilk is in some instances very well tolerated, and is apt to be a useful food in the later stages of the disease where the in-

flammatory conditions have subsided and where we are confronted mainly with retardation in growth. I have used lactobacilline, milk, and also tablets of lactobacillus, but have not been able to observe any special benefits from their use.

The pharmacological measures to be employed in the course of the treatment of infantilism are so subordinated to those of environment and diet that it seems hardly necessary to discuss them here. It seems in general best to avoid the use of cathartics. The employment of iron and arsenical tonics by mouth appears to be of doubtful utility, especially during the active period of the disease. The use of cacodylate of soda subcutaneously might be worth trying where there is considerable anemia. The possibility of employing eserine to reduce congestion in the digestive tract is perhaps worth more consideration than it has received.

It should be entirely clear that the state of intestinal infantilism is a highly refractory one and not likely to be followed by a return to normal growth except as the result of discriminating therapeutic interference. Among the poorer classes there are probably a good many deaths from the acute or subacute infections which lead to infantilism, but among the well-to-do population who are willing to take pains with their children deaths are very few, either in the initial acute and subacute stages or in the later stages. It is to be expected that a permanently undersized individual will be the outcome even in the most favorably progressing instances of the severe form of infantilism. In one of the ten instances that I have followed there was excellent compensation after the tenth year, so that the outcome was a young adult of normal size. In this case the retardation of growth was almost complete during four or five years. In a good many cases the outcome is a state of marked dwarfism, and there can be little doubt that a certain proportion of dwarfs in the community arise through the persistence of intestinal infantilism. Aside from cretinism, it may be that this is the most common cause of dwarfism. It is important to note that the retardation in physical development is not incompatible with a high degree of mental culture.

It is also to be remembered that temporary relapses are very common in the course of infantilism, even when the greatest care

is being taken to prevent them. Such relapses on the part of the digestive apparatus may occur while the patient is upon a diet which has been well tolerated for weeks or even for months. The most frequent cause of relapse is the attempt to encourage growth through the too free use of carbohydrates. When the relapse occurs the feces become voluminous, lose their conglomerate appearance, and show an excess of fat or an excess of acid due to the fermentation of carbohydrates. In persistent relapses an increase in the number of organisms of the *B. infantilis* and *B. bifidus* types can often be determined.

It should be evident that treatment of these cases of infantilism requires the utmost tact and patience on the part of the physician and the intelligent confidence of the parents. For obvious reasons it is of the first importance that the physician should recognize the nature of these cases at the earliest possible time in order that he may prepare the parents for the long, perplexing, and often discouraging course of events which necessarily attends even the most favorable progress of these unique types of digestive disorder.

NOTE ON THE EFFECTS OF FEEDING FERMENTED CORN TO MONKEYS.

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Experiments were made in the feeding of fermented corn to nine rhesus monkeys. In several instances preliminary observations were made on the effects of feeding ordinary commercial uncooked corn meal, which was surprisingly well taken with water as an exclusive diet during weeks and even months. The fermented corn meal used in the feeding experiments was of three types: (A) corn meal fermented through the addition of fecal bacteria from a severe case of pellagra; (B) corn meal fermented two days in the incubator through the addition of water; (C) corn meal fermented as in (B) except for the addition of corn meal suspected of being responsible for an outbreak of pellagra. An experiment made with the corn meal fermented with pellagra feces (Type A) was abandoned after many weeks as it gave negative results. Animals fed for weeks or months on plain fermented corn meal (Type B) sooner or later developed intestinal disturbance and prostration and ultimately died. Animals fed with corn meal fermented with suspected pellagra corn (Type C) reacted as with Type B, except more rapidly. In all cases a few or many small ulcers were found in the colon, and these were the only constant lesions. Two animals had pneumonia and two developed an intussusception, but the conclusion was reached that most of the animals died as the result of an intoxication.

Corn meal fermented as in Type C was extracted with alcohol and acetone, from which was obtained a material markedly toxic in small quantities for guinea-pigs. The nature of the toxic substance or substances is being investigated. In no case were any symptoms observed which suggested pellagra in man.

TOXEMIC JAUNDICE.

ABSTRACT.

By DAVID RIESMAN, M.D.,
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A SERIES of interesting cases of jaundice not due to obstruction has come under my observation within recent years. In some of the cases the absence of any mechanical obstruction in the bile ducts was inferred from the clinical symptoms, there being no autopsy. The jaundice was most frequent in pneumonia. I have no definite statistics, but by a curious coincidence the first four cases of pneumonia admitted to my wards in the Philadelphia General Hospital during the last winter had jaundice. If the eyes are always carefully examined, I believe that no less than a third of all cases of lobar pneumonia will be found to have more or less icterus. One of the four cases just mentioned, in which the jaundice had been very marked, the sputum even being bile-stained, came to autopsy. The liver was enlarged, of a greenish yellow color, and the surface of the section dotted with small red pin points. The bile ducts were patulous; the bile thick and black. On microscopic examination, the principal change was a peculiar loosening up of the hepatic texture, resulting in the separation of the liver cells one from the other. The bile ducts were few in number in the sections and presented nothing strikingly abnormal.

To the same group, namely, that of jaundice in infectious diseases, belongs a case of septicemia with deep jaundice in a young man, which was the sequel of a dental abscess. At the autopsy the liver presented nothing of note; the bile ducts were patulous; the sections were, unfortunately, lost.

In another class of non-obstructive jaundice is acute yellow atrophy, of which three cases have come under my observation in recent years. Two are of particular interest in that they occurred in Austrian Slavs living on the same street, and employed in the same factory. The cases were not synchronous; one was seen in consultation at his home, and the other several months later as a hospital patient. Both died after a short illness, and no autopsy was obtained. The factory in which they were employed was devoted to the making of articles of bone, such as chessmen, bobbins, combs, etc. It was well ventilated and had every mark of being in a sanitary condition. No other cases of jaundice or of serious illness had occurred among the workmen. The personal histories of the patients also threw no light on the causation of the jaundice.

A third case of acute yellow atrophy was that of a colored man admitted to the Philadelphia General Hospital on May 3, 1909, in an unconscious state. Death occurred two days later. He had been employed in an artificial ice factory. The liver, both on naked eye and on microscopic examination, showed the characteristic lesions of acute yellow atrophy. (A water-color drawing and microphotographs were shown.)

The next case is one not easily classified. The patient was an Austrian Slav, who was admitted to the Philadelphia General Hospital with the deepest jaundice I have ever seen. Beyond the fact that he had been ill a few days, no history was obtainable. The clinical symptoms suggested acute yellow atrophy, but as autopsy the liver was found normal in size, of a dark color, with patulous ducts, and without any evidences of necrosis. The microscopic examination showed individualization of the liver cells, similar to that described as occurring in the case of pneumonia. (Microphotographs were shown.)

Another very remarkable case was seen at the Philadelphia General Hospital. A woman, aged thirty years, was admitted with delirium and mild but distinct jaundice. After a careful study, the details of which cannot be given in this abstract, a diagnosis of acute miliary tuberculosis and enlargement of the liver was made. I had no clear idea as to the nature of the hepatic enlargement. At autopsy, miliary tuberculosis was found, and a liver of enormous size, com-

pletely transformed into fat. The organ was of a butter-yellow color, soft and doughy. Microscopic examination did not reveal a single intact hepatic cell, the sections showing the characteristic areolar appearance of fatty liver.

In none of the cases described above was the jaundice due to an obstruction of the excretory bile ducts of the liver. What, then, was the cause of the jaundice? The question is a difficult one. The older authorities, not finding any obstruction, established the group of hematogenous jaundice, that is, a jaundice due to bile formation in the blood. The researches of Stadelmann, Affanassiew, Hunter, and others seem, however, to demonstrate the fact that jaundice is always in its essence hepatogenous in origin. Rolleston looks upon the presence of bile pigment granules in the liver cells as proof positive of the hepatic origin of the pigment; but it is doubtful whether such a conclusion can be drawn, for if the bile were made anywhere else, it might readily be deposited in the liver.

Assuming that in toxemic jaundice, as in any other jaundice, the bile is made in the liver, what explains the failure of all of it to pass out through the normal channels? That some passes out is proved by the presence of bile in the feces. Hunter, from experiments with icterogenic poisons, particularly toluylendiamin, concludes that there is a thickening of the bile and a catarrhal swelling of the finer bile capillaries; in other words, that there is an obstruction, but that it is deep within the acini of the liver. Eppinger reached a similar conclusion upon finding dilatation of the delicate interhepatic and intrahepatic bile channels described by him, as well as obstruction by biliary thrombi. I have no doubt that this theory explains many cases of toxemic jaundice, but I would venture the hypothesis that in some instances, instead of a catarrhal swelling of the bile passages, there is merely a functional disturbance, leading to a change in the pressure relations within the liver, whereby a reversal of the bile flow is produced.

The peculiar jaundice described by French writers as congenital, acquired, and familial hemolytic icterus, deserves a word of mention, especially because it has reopened the subject, believed to be closed, of a hematogenous origin of jaundice. Studies of the blood in hemo-

lytic jaundice have revealed a peculiar fragility of the red corpuscles which causes them to disintegrate readily. This fragility accounts for the anemia present in cases of hemolytic jaundice. Widal believes that the pigment has a parahepatic origin. Oettinger, however, without denying this possibility, inclines to the view that the pigment is hepatogenous; that bile is produced in excess as a result of the inordinate amount of destroyed hemoglobin brought to the liver. To my mind this is the more reasonable hypothesis. It is hardly fair to conclude that because the liver is histologically normal the bile pigment found in the tissues cannot have been made there.

Toxemic jaundice is in its essence hepatogenous, and has as its cause either a swelling of the finest bile capillaries or a change in the osmotic pressure bringing about a reversal of the bile flow. In either case an additional factor is generally operative, namely, the presence of an excessive amount of raw material for the manufacture of bile, supplied to the liver in consequence of a massive blood obstruction.

DISCUSSION.

Dr. William S. Thayer: I am very much interested in the paper just read, interested, in the first place, to hear Dr. Riesman say the jaundice of pneumonia, for instance, was hemolytic in origin. For some time I have been struck by the fact that jaundice in pneumonia occurred often in healthy, vigorous individuals who, even a few days after the onset of the disease showed a number of red blood corpuscles not much over 4,000,000. Now, at the time of the onset the blood count was probably 5,500,000 or more. That means that these patients have lost in two or three days as many red blood corpuscles as they would have lost in a really severe malarial infection, or, for instance, in typhoid fever in the course of three or four weeks. Such clinical evidence suggests that the jaundice of pneumonia is due primarily to increased blood destruction during the early days of the disease.

Dr. S. J. Meltzer: Dr. Thayer says that most of the cases of pneumonia are more or less jaundiced. Older physicians will remember that the term "biliary pneumonia" was applied to cases of pneumonia complicated with jaundice; the prognosis of these cases was considered grave. There is perhaps, some foundation for this gloomy view. It was recently found that bile is an excellent solvent for pneumococci. In cases of pneumonia in which a good deal of bile is present in the circulation, perhaps, indeed, a larger number of bacteria become dissolved and more endotoxins liberated; hence the greater danger.

ANURIA; FIVE DAYS; POSTSCARLATINAL; BOY, AGED THREE AND ONE-HALF YEARS; RECOVERY.

By W. P. NORTHRUP, M.D.,
NEW YORK.

There are two reasons for reporting this case; one is that it is rare, and the other, that it was exceptionally well observed.

There are but few cases on record. One case of eight and one of twenty-five days' anuria, with recovery, after scarlet fever, have been reported, and seem to to be authentic. Both were cared for by the parents and servants, and watched by physicians. However, in the first case two warm tub baths were administered daily by these "careful parents" (in the eight-day case), and though they were careful, and watched with fond anxiety for the passage of urine, knowing full well what it would mean, they saw none pass, either in the bath or elsewhere.

I desire to give the present case its full value, and therefore state that the patient was the grandson of our colleague, Dr. S. J. Meltzer, the son of Dr. John Auer, both of the Rockefeller Institute. Furthermore, the mother, Mrs. Auer, is a medical graduate and opthalmologist. When I have added that the patient was the only son and the only grandson, I think I have sufficiently emphasized the fact that he was closely observed, and that he positively passed no urine without it being noted. A trained nurse was also in attendance, and one or both parents, night and day.

The case is rare, and it is authentic. Its history may be divided into three periods:

First period of twelve days: Boy aged three and one-half years; scarlet fever, usual eruption; severe angina with pseudomembrane on tonsils and fauces; diptheria antitoxin, 5000 units; no bacilli

diphtheriæ found subsequently. The antitoxin was made by Mulford, and the "whole" antitoxin was used; it was injected partly intramuscular in the scapular region. Half an hour after the injection the boy is said to have had a moderate chill, and become moderately cyanotic, in partial collapse. From this he rallied without serious trouble. For three or four days, beginning almost immediately after administration, he had an urticarial rash. It appeared in great areas over his body, appearing and disappearing. Temperature, 102°, then 105.5° once and 105° four times during this period. Pulse, 120 to 160. Urine passed was recorded daily: quality fair, quantity 525, 525, 750, 875, 300, and 50 c.c.; trace of albumin; no casts. A soft blowing murmur was noted at the apex.

The second period consisted of five days, during which time I saw him daily.

On my first visit the urine passed up to noon was 50 c.c. Temperature was 104°. The questions before the consultation were:

Why was the temperature so high on the tenth day?

What was the significance of the heart murmur?

What about the diminishing urine?

The abdomen was distended; the throat red and swollen; the tongue bright red, "varnished." Neither pneumonia nor condition of ears could explain the temperature of the rapid respiration. The throat was deep red and swollen. Urine: alkaline, and contained a trace of albumin; no casts; 1015 to 1020; few blood cells; few leukocytes; enormous number of renal cells. (Examined by Dr. Auer.) It was thought that the throat and intestinal tract was responsible for most of the febrile reaction. A full dose of castor oil was advised. The urine for half a day was still 50 c.c. The temperature fell after taking the castor oil to 100°, and the second day touched normal. A few drops of urine passed; slight edema of the face and feet.

Second day, no urine was passed; none in the bladder.

Third day, no urine.

I had had experience with suppression for fifty hours and seventy-two hours, and had words of encouragement. I assured the parents and friends that the kidneys would resume their functions again, and that when they did, the first urine passed would probably be

of beef-tea consistence and bloody for some days, gradually becoming more and more copious. Such is usual with scarlatinal nephritis.

Fourth day, no urine was passed. The boy was becoming so edematous and waterlogged that he could not be lifted. He flattened out on the bed immovable, his eyes almost closed; hands, feet and legs swollen; skin shining; ascites. Yet he had no symptom of uremia; no nervous signs; no twitching; not dopey; no insomnia; vision clear; no headache; no vomiting; breath of normal odor; no clammy perspiration; skin natural. There was no delirium; pulse tension not increased; tranquil, not somnolent; slept naturally; temperature not above 100°; he just thickened and flattened over the bed.

Fifth day, no urine; general anasarca; ascites, heavily water-soaked. At this time no one could offer further prognostications. The favorable features were the absence of all nervous signs, yet it was hoped that in some way the kidneys would resume their functions. It was argued that, the patient being a child, "there is nothing a child cannot do." We exhausted all resources, traditional and new. Nothing medical appeared to have the slightest effect upon the renal functions. The general impression was of some inhibition upon the action of the kidneys, whereby they simply lay inactive in the bottom of the abdomen. The mental atmosphere of the household may well be imagined.

To summarize this second period: For five full days the boy passed into absorbent cotton only a few drops of urine—not sufficient to measure. He had no symptoms of uremia, but became waterlogged.

Third period. On the afternoon of the fifth completed day, or beginning of the sixth, the patient passed 40 c.c. urine. The amounts were in drams—one, one-half, two, one, etc.—passed in spurts. The next day he passed 300 c.c., beginning (at one time) with one ounce. The next successive days 600, 1000, 1750, 2100 c.c., etc. The first urine passed was rich in albumin, reddish, and contained a large number of granular casts. It was not of the usual beef-tea-like fluid.

The boy is now entirely well, no albumin, no heart murmur,

eardrum healthy. In short, he is perfectly healthy, and shows no trace of his illness.

Points suggested for discussion:

1. Was there purely a toxic inhibition of the kidney functions?

2. Was there a possible swelling of the kidney within its capsule, prohibiting function, and was this in anyway analogous to the urticarial swelling of the skin? Angiomatous?

3. Would anyone nowadays, in a similar case, suggest splitting the capsule surgically? The present case recovered, but would one again wait five days?

Summary.—1. It is an authentic case of anuria of five days' duration.

2. The case is rare, but not unique.

3. The probable cause is toxic inhibition.

4. Inflammation of the kidneys, as evidenced by the urine, was not severe. Recovery was prompt and complete.

5. There were no uremic symptoms.

6. Whether there was any relation between the excessive urticaria of the skin and the antitoxin (diptheritic) is merely conjectural.

7. The kidneys seemed to lie in the bottom of the abdomen inactive, while the body became waterlogged.

DISCUSSION.

Dr. Milton H. Fussell: I can recall a case of anuria extending over a long period of time, a period, I believe, of four days. This child began to be ill with some simple febrile attack of uncertain character. He soon began to pass urine in small quantities, and then none was passed at all for four days. He then began to pass urine in about the same way as in Dr. Northrup's case, the amount gradually increasing, until the child was passing excessive quantities. There was no anasarca. The child later died of a general miliary tuberculosis. An autopsy was performed and sections of the kidney were made. Congenital syphilis was thought of, but there was nothing to be found in the kidney which indicated why this child should go for such a long period of time with anuria. Unfortunately, the child was not observed with the same accuracy as was Dr. Northrup's. This case occurred in a poor family, and while the woman was not particularly intelligent, I believe she told the truth when she stated that the

child had not passed any water during that period. I saw the child myself several times during that time.

Dr. S. J. Meltzer: I made the suggestion that in this case perhaps we did not deal with a scarlatinal nephritis, but with an anuria caused by a compression of the tubuli and glomeruli brought about by an urticaria-like interstitial or subepithelial infiltration, and which, like the urticaria of the skin, was due to the injection of the serum.

Dr. William S. Thayer: I should like to ask Dr. Northrup whether he has ever observed in his practice instances of general anasarca, ascites, and hydrothorax, with diminution in the quantity of urine but without apparent renal symptoms and without albumin in the urine. I recall a remarkable case which I saw several years ago with Dr. Theodore Dunham. This was a child five or six years of age, who for a period of two months at least was absolutely waterlogged and yet without a single grave constitutional symptom, and without any abnormal signs in the urine excepting a reduction in its quantity. There was marked general anasarca and ascites, and the appearance was quite like that of a case of hydropic nephritis. We were entirely at a loss to account for the condition, and could only say to the family that the child seemed so well and bright that we felt that it must recover. It did recover completely. This is the only instance of this sort that I have ever seen. I should like to ask Dr. Northrup if he ever met with a similar case?

Dr. Frederick C. Shattuck: I should like to ask how frequent polyuria may be as a sequel of scarlet fever. I recall the case of an adult many years ago, a young man of anything but nervous temperament, who had a tremendous polyuria coincident with convalescence from scarlet fever. This was a sure symptom or sign of any renal disturbance.

Dr. R. D. Rudolf: I should like to ask Dr. Northrup if the symptoms and signs of nephritis were present before the administration of the antitoxin. We have had at the Children's Hospital in Toronto several patients who have suffered from severe exacerbations of nephritis, with anuria, following the administration of antitoxin; so much so that the routine prophylactic dose of 500 units which is given to every child upon administration is omitted in those cases which show evidence of nephritis.

Dr. Northrup: There were no signs of nephritis before the administration of the antitoxin. The boy was a very healthy one. Like Dr. Thayer, I have never seen anything like this before.

I cannot at this moment answer Dr. Shattuck's question regarding excessive amounts of urine following attacks of scarlet fever. After the child became ill he presented the beef-tea urine, then it became yellow. It is a unique case.

In the cases reported in the literature there are so many weak places. In some it is recorded that the patients were given tub baths every day for periods of

eight days or more, and this admits of opportunity of error, even though the cases were most carefully observed. One twenty-five day case has been reported in English practice. Three physicians were at first very skeptical, and then afterward became convinced and stated that the patient had gone twenty-five days without passing water. In this case there was the "very devoted nurse" and "very devoted mother." All the cases reported, I am convinced, are very rare. Hosts of cases die at different periods, but we are interested in those that recover after such prolonged periods of anuria.

Dr. Francis P. Kinnicutt: I should like to know if the urticaria was very severe?

Dr. Northrup: Yes; just like maps of North and South America. It appeared on the back. Even the eyes were closed. This extended over a period of from three to four days.

Dr. Kinnicutt: Were there any gastric symptoms?

Dr. Northrup: During five days, none. One of the best things on this subject is a monograph by Dr. E. P. Fowler, of New York, published in New York in 1881, on "Suppression of Urine," in which he brings up these points. The article contains the reports of the two recoveries referred to.

PECULIAR ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES IN A CASE OF SEVERE ANEMIA.

By JAMES B. HERRICK, M.D.,
CHICAGO.

This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. I report some details that may seem non-essential, thinking that if a similar blood condition is found in some other case, a comparison of clinical conditions may help in solving the problem.

The patient was an intelligent negro, aged twenty years, who had been in the United Stated three months, during which time he was a student in one of the professional schools in Chicago. His former residence had been Grenada, West Indies, where he had been born and brought up, one of a family of four children, all living, and all well with the exception of himself. His mother was living and in good health; his father had died of an accident. At the age of ten years the patient had yaws. This was a common disease in the locality where he lived. The lesions as he described them had been pustular, with formation of ulcers and scabs. On healing, scars, many of which he pointed out, were left. Some of the ulcers had been as large as a silver quarter of a dollar. The disease lasted about one year and during this time he had felt somewhat weak and indisposed. Most of the ulcers had been on the legs, and the patient himself had thought this location of the lesions might have been due to the bruises and scratches that were frequently produced as he

ran about, a barefoot boy, through the streets and the brush. He was sure that he had never had "ground itch," though he said it was not uncommon in Grenada. He had attended school up to the age of seventeen. Since leaving school, that is, for the past three years, he had felt a disinclination to take exercise. For about a year he had noticed some palpitation and shortness of breath, which he had attributed to excessive smoking. There had been times when he thought he was bilious and when the whites of the eyes had been tinged with yellow. At such times he had not had any pain, chill, or fever. Three years ago he had had a purulent discharge from the right ear lasting six months. He had had no diarrheas and no hemorrhages at any time. He denied syphilis and gonorrhea. There was never any rheumatism or other joint trouble. On landing in New York, in September, 1904, he had a sore on one ankle for which he consulted a physician. Tincture of iodine was applied and in a week the sore had healed, leaving a scar similar to the others on the limbs.

For the past five weeks he had been coughing. Two days ago he had "taken cold," his cough had grown worse, and he had a slight chill followed by fever. It was this cough and fever for which he wished treatment at the hospital and of which he chiefly complained, though he mentioned also that he felt weak and dizzy, had headache and catarrh of the nose.

Examination showed him to be a young man of typical negro facies, with black curly hair. He was fairly well developed physically, and was bright and intelligent. There was a tinge of yellow in the scleræ and the visible mucous membranes were pale. The eyes were normal; the pupils showed prompt reaction to light and in accommodation. The hearing was good, there was no discharge from the ear. The nose showed chronic and acute rhinitis. The tongue was coated, the pharynx slightly reddened; no scars or other lesions were found here. The cervical glands were definitely enlarged, hard, and not painful. The axillary, inguinal, and epitrochlear glands were also enlarged, some in the axilla being of the size of almonds. Over the chest and abdomen were several good-sized leucodermatous patches, the intervening skin being rather deeply pigmented. The scars to which we have referred were nearly all located on the legs

and thighs, some in the former location being as much as 3 cm. in diameter. There were perhaps twenty scars in all. They were rounded or oval, sometimes of irregular contour, the edges clean-cut; some were like tissue paper or thin parchment to the touch, and were lighter in color than the surrounding skin. They were strikingly like scars often seen as the result of syphillis.

The chest was well formed. There was fair expansion. Numerous rales, mostly of the moist variety, were heard scattered throughout the chest, especially posteriorly. There was a slight relative dulness over the base of either lung behind. The heart was enlarged to the left, the apex impulse being in the sixth interspace one inch to the left of the left mamillary line. There was but a slight increase in the dulness to the right. A soft systolic murmur, not well transmitted in any direction, was heard over the base of the heart. A faint systolic murmur, or perhaps one would better call it an impure first tone, was heard at the apex. The heart's action reminded one of a heart under strong stimulation though no history of ingestion of a stimulant of any kind was obtainable. Basedow's findings were not to be made out. The pulse was of good quality and of fair volume. The abdomen was not distended, nor was it tender. Neither spleen nor liver could be palpated. There was no tenderness over the gall-bladder region. The genitalia were normal. The patellar reflexes were sluggish. There was no ataxia and there were no sensory disturbances.

The temperature on admission was 101°. It varied between 99° and 101° for four days, then gradually subsided, though for the next three weeks it was often found between 99° and 100°, though with no regularity. The pulse varied from 64 to 104, averaging about 80. There was never any rapid breathing. The urine was amber in color, specific gravity 1010 to 1014, slightly increased in amount—2000 c.c.—acid, contained a distinct trace of serum albumin, a few granular and hyaline casts. This represents the average of several examinations. The urine on admission had a trace of bile. December 28, urinary examinations for hemoglobin and hematoporphyrin were made and none found. No tubercle bacilli were discovered in the sputum.

The blood count on December 26, 1904, was: Red corpuscles,

2,570,000; white corpuscles, 40,000; hemoglobin (Dare), 40 per cent.; color index, 0.78.

December 31, the count was as follows: Erythrocytes, 2,880,000; leukocytes, 15,250; hemoglobin, 50 per cent. (Dare).

The red corpuscles varied much in size, many microcytes being seen and some macrocytes. Polychromatophilia was present. Nucleated reds were numerous, 74 being seen in a count of 200 leukocytes, there being about 5000 to the cubic millimeter. The shape of the reds was very irregular, but what especially attracted attention was the large number of thin, elongated, sickle-shaped and crescent-shaped forms. These were seen in fresh specimens no matter in what way the blood was spread upon the slide, and they were seen also in specimens fixed by heat, by alcohol and ether, and stained with the Ehrlich triacid stain as well as with control stains. They were not seen in specimens of blood taken at the same time from other individuals and prepared under exactly similar conditions. They were surely not artefacts, nor were they any form of parasite. In staining reactions they were exactly like their neighbors, the ordinary red corpuscles, though many took the stain heavily. In a few of the elongated forms a nucleus was seen. In the fresh specimen, where there was a slight current in the blood before it had become entirely quiet, all of the red corpuscles, the elongated forms as well as those of ordinary form, seemed to be unusually pliable and flexible, bending and twisting in a remarkable manner as they bumped against each other or crowded through a narrow space and seeming almost rubber-like in their elastic resumption of the former shape. One got the impression that the flattened red disks might, by reason of unusual pliability, be rolled up as it were into a long narrow bundle. Once or twice I saw a corpuscle of ordinary form turn in such a way as to be seen on edge when its appearance was suggestive of these peculiar forms.

The white corpuscles were made up of polymorphonuclear neutrophiles, 72 per cent.; small mononuclear lymphocytes, 15 per cent.; large mononuclear forms, 7 per cent.; polymorphonuclear eosinophiles, 5 per cent.; myelocytes (?), 1 per cent. Many polymorphonuclear cells and some mononuclear forms contained basophilic granules (Neusser's polynuclear basophiles?). In overheated

specimens especially, a number of cells with shadowy outlines and staining but slightly were seen. These resembled white cells.

The stools were examined not only as a matter of routine, but because of the possibility of detecting the presence of some parasite that might explain the eosinophilia, leukocytosis, and anemia, a possibility not at all unlikely in one coming from the tropics and who had lived where "ground itch" was a common occurrence. Many stools were thoroughly studied. Considerable mucus was found in some of the stools passed soon after admission and some of the mucus was blood stained. No blood was found in the interior of the fecal masses. On two occasions preceding the giving of the thymol a body was found resembling almost typically the egg of anchylostoma duodenale. Portions of the stools were inoculated but no embryos were to be made out. Thymol was given, but neither eggs nor embryos could be found in the stools following its administration.

Under treatment, consisting of rest, nourishing food, and syrup of the iodide of iron, the fever and rales disappeared, the glands became smaller, the blood improved in quality, and the patient left the hospital after a four-weeks stay declaring that he felt well. The possible therapeutic influence of the thymol must also not be overlooked. The blood at this time showed 3,900,000 red corpuscles, 15,000 whites, 58 per cent. hemoglobin. There was still to be seen a tendency to the peculiar crescent-shape in the red corpuscles, though this was by no means so noticeable as before. Nucleated reds were present, though in smaller numbers. Eosinophiles were found as before making up about 5 per cent. of the total number of leukocytes.

We were at a loss to account for this peculiar complexus of symptoms, a condition evidently chronic, as revealed by his history of the past three years, with yaws and suppurating otitis as predecessors, yet with acute exacerbations, a condition not clearly explained on the basis of an organic lesion in any one organ yet showing cardiac enlargement, albuminuria and cylindruria, general adenopathy, icterus, with a secondary anemia not remarkable for the great reduction in red corpuscles or hemoglobin, but strikingly atypical in the large number of nucleated red corpuscles of the normoblastic type and in the tendency of the erythrocyte to assume a

slender sickle-shape. The leukocytosis with a rather high eosinophile count was also to be noted.

An attempt was made to keep track of the patient, and while he was never afterward under my professional care, he was twice seen by myself and several times by Dr. E. E. Irons, whose notes and blood examinations are here incorporated.

January, 1906. In a hospital for a few days with bronchitis. Rapid recovery.

March 7, 1906. In bed with fever, bronchitis; feels weak. No diarrhœa. Red blood corpuscles, 2,700,000; whites, 30,050. Hemoglobin, 55 per cent. Blood shows many elongated erythrocytes, a few microcytes. The elongated and spindle-forms seemed to stain more darkly than the normal round red corpuscles. No parasites were seen. The differential count of the white cells showed polynuclear neutrophiles, 58; large mononuclear, 12; small mononuclear, 22; eosinophiles, 7; myelocytes, 1. There were 2279 normoblasts to the cubic millimeter.

A count on March 14, 1906, showed an increase in the reds, a lessening of the whites, but was in other respects practically the same. The stool was normal in appearance, formed, yellowish brown, and no blood or eggs were found. The urine was acid, clear, with no blood or abnormal pigment. There was a trace of albumin, and several granular and hyaline casts were found.

In May, 1906, he was seen by Dr. Irons, who found him with some fluid in the left knee-joint; the temperature was 100°. Gonorrhœa was denied. The patient ascribed the joint trouble to a wrench of the knee a few days before. He recovered after ten days of rest in bed.

In April, 1907, the young man reported that he had been laid up in a hospital from December 26, 1906, to February 26, 1907, with what he called muscular rheumatism. His illness had begun with malaise, pain in the back, the muscles of the legs and arms. He had had a slight fever and was pale. A few days before this illness he had suffered from one of his "bilious" attacks, in which he had had quite severe epigastric pain, had vomited and had later noticed that the urine was dark and that the scleræ was yellowish, though he was inclined to think the icteric hue had been present before the

onset of the pain. He was still, he said, somewhat short of breath, but in other respects felt quite well.

Since then I have never seen nor heard from him.

No conclusions can be drawn from this case. Not even a definite diagnosis can be made. Syphilis is suggested by many of the facts, such as adenopathy and the condition of the heart and kidneys; it might explain the anemia, the arthritis and perhaps also the temperature, cough and attacks of pain resembling hepatic or gall-bladder disease, for as is well known visceral syphilis may furnish a most bizarre group of symptoms. The Wassermann test was not in use at this time. The scars said to have been from the yaws were like those left by syphilis.

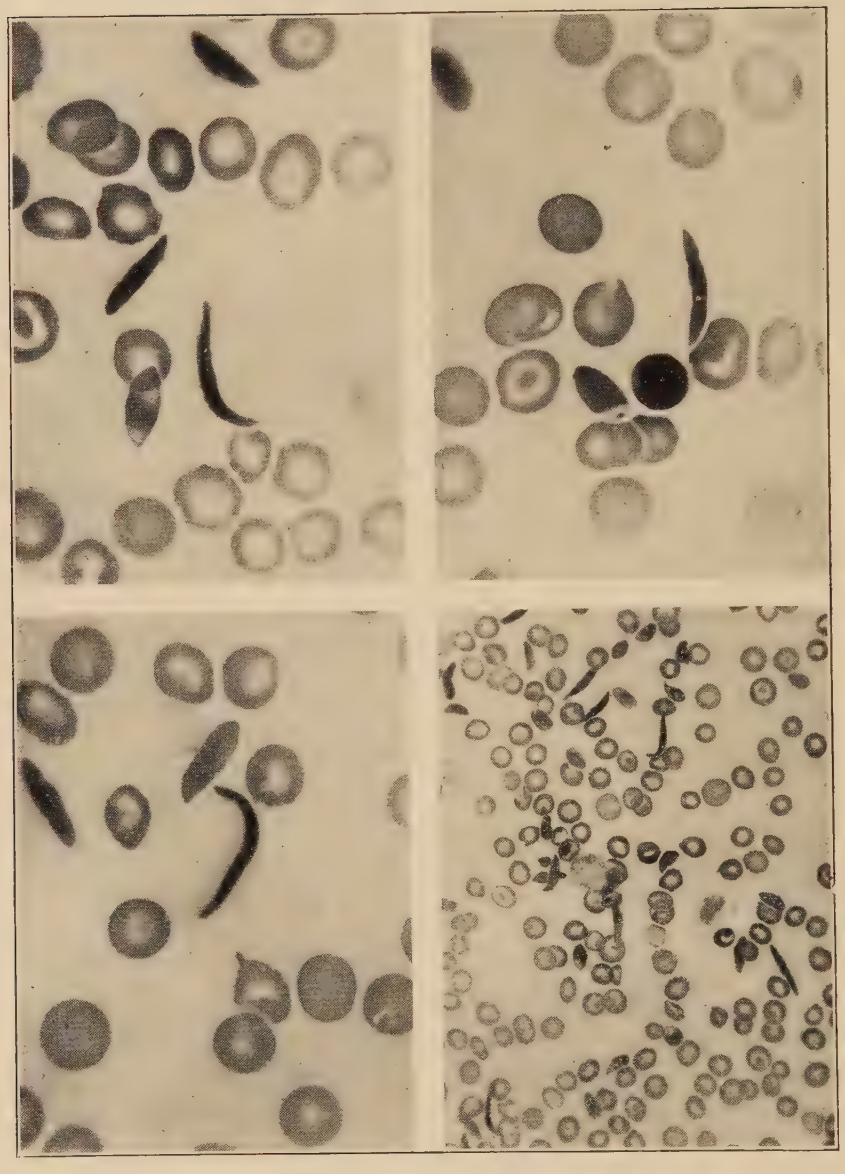
The patient coming from the tropics, one thought of intestinal parasites such as uncinaria as a possible explanation of the anemia and the eosinophilia. What were thought to be eggs were found on one occasion only and after thymol there was temporary improvement.

The odd blood picture made one examine for possible toxic effects of the coal tar preparations, but neither from the history nor from the examination of the urine was there any evidence that such drugs were habitually taken. We were at this time particularly interested in the subject of chronic acetanilid intoxication, as well as in uncinariasis, having just had a case of each of these interesting conditions under observation, so that we were on the lookout for such out-of-the-way diseases.

The question of diagnosis must remain an open one unless reports of other similar cases with the same peculiar blood picture shall clear up this feature.

Schleip, in his *Atlas*, pictures fresh unstained preparations of red blood corpuscles made by his method of diluting the blood 1 to 10 with physiological salt solution and examining with the aid of the hanging drop chamber. Some of the corpuscles remind one a little of these forms I have described. Yet they are not exactly the same.

Professor Hektoen showed me a specimen that he had encountered in the course of some of his hematological work that most closely resembled these forms. This preparation was one where washed



The photomicrographs show the peculiar elongated forms of the red corpuscles. Occasional shadow forms are seen with a few nucleated reds. The variations in shape and size are best made out in the low power figure. The relatively large number of white corpuscles and of normoblasts is not well shown by these particular fields.

human corpuscles were suspended in a $\frac{n}{8}$ solution of cane sugar. But neither Dr. Hektoen nor I have been able to reproduce the exact picture again, though using cane sugar solution of the same strength. This, while suggesting that the chemical composition of the fluid suspending the corpuscles may have something to do with these peculiar formations, perhaps suggests more strongly that some unrecognized change in the composition of the corpuscles itself may be the determining factor.

PERNICIOUS ANEMIA.

A CASE WITH A REMISSION FOR SEVENTEEN YEARS. RELAPSE AND DEATH.

By ALEXANDER McPHEDRAN, M.D.,
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The object of this article is chiefly to record a case in which there was a remarkably long period of complete remission of symptoms, amounting to a cure for some sixteen years, with final relapse showing all the characteristic symptoms and pursuing a truly progressive course to a fatal ending.

The case, that of a physician, was one of five reported in the *Medical News*, October 11, 1890. At that time Dr. P., aged forty-nine years, was engaged in a large country practice. He had been losing strength and growing anemic for a year or two. He became much worse and was compelled to cease work in the Spring of 1889; he soon became very ill, with a temperature of 104° F. and marked delirium. There was severe vomiting and diarrhœa. The skin was very pale, but with a decided lemon tinge. The blood showed the characteristic appearances of pernicious anemia; 730,000 red blood corpuscles per cubic millimeter. There were retinal hemorrhages in both eyes. He had recurrent chills irregularly, with high temperature, delirium, vomiting, and diarrhœa for nearly three weeks, after which he began to improve, slowly at first, but later more rapidly. Arsenic was given early and gradually increased until 45 minims of Fowler's solution was taken daily. In a month the corpuscles reached 1,700,000, and at the end of another month 3,250,000. His general condition was correspondingly improved. Five months later he was apparently quite recovered and able to

resume his practice. His blood contained then nearly, if not quite, the usual number of practically normal red corpuscles per cubic millimeter. He remained well and in constant practice until the autumn of 1906, when he found himself growing weak and unequal to his work. When examined in the following March, 1907, he was very weak, the body surface markedly yellowish, the appetite poor, the bowels constipated, with occasional diarrhœa. The blood contained 1,926,000 red corpuscles per cubic millimeter, of large size generally, poikilocytosis marked, and both normablasts and megaloblasts being present. Hemoglobin was 39 per cent.; white corpuscles, 4200; lymphocytes over 30 per cent.; few eosinophiles. He improved rapidly and by the end of a month there were over 3,000,000 red corpuscles per cubic millimeter; no megaloblasts were found and the eosinophiles were numerous.

In the early summer there were over 4,000,000 red corpuscles per cubic millimeter, and he was feeling correspondingly improved. He went to the Canadian Northwest as far as the Rocky Mountains in the summer. While travelling, vomiting and diarrhœa were troublesome, and he became much prostrated. With rest he improved steadily and was fairly well on his return in November. He was not seen until January, 1908. He looked well, although his strength was failing since his return from the West; appetite was fair; tongue clean, no stomatitis, gums healthy, teeth having been removed some years previously. He had some diarrhœa for a day or two, about every two weeks; stools liquid but not offensive. The blood contained about 3,500,000 red corpuscles per cubic millimeter, showing only slight variation in size and shape. From that time on his condition became generally worse, with slight improvement for a few days from time to time. He had frequent recurrences of vomiting and diarrhœa, the stools being copious and liquid. During the month before he died he was scarcely more than semiconscious; his general condition was that of marked pernicious anemia. Death took place May 17, 1908, at the age of sixty-eight, over twenty-years after the first symptoms of his first attack showed themselves. He recovered from the first attack in the autumn of 1889 and continued in good health until 1906, a period of seventeen years. During these years there was no opportunity for making an examination of his

blood or general condition, as he felt in very good health and his capacity for work was excellent. He therefore considered examinations unnecessary. After his death, unfortunately, there was no opportunity for an autopsy.

So far as I can determine from the literature of pernicious anemia, the duration of the disease and length of complete remission during which he was in good health are much the longest on record. The recovery from the first attack had been of such long duration that I had for years regarded it one of complete and permanent recovery. "Call no man happy until he is dead" is certainly applicable to pernicious anemia. Had he died a year or two earlier from some intercurrent illness, such as pneumonia, or by an accident, his case could, with good reason, have been recorded as one of permanent recovery from pernicious anemia.

As to the justice of such a conclusion, much will depend on the definition we give of a recovery. In the acute diseases, and in many chronic ones, recovery takes place and later another attack occurs from a subsequent infection, as, *e. g.*, in pneumonia, erysipelas, and malaria among the acute, and tuberculosis and even syphilis among the chronic diseases. If we apply the same reasoning to pernicious anemia, some cases doubtless do recover, and this case should be included in the list, as there is scarcely a doubt that his blood would have shown a normal appearance during those years of good health, had it been examined.

It is probable that all the cases of permanent recovery on record have also suffered a relapse if they were not cut off by some intercurrent disease. One can scarcely agree with the statement that "When a patient has been six years free from trouble it seems safe to conclude that no recurrence will occur," or that any such group of cases demonstrate the possibility of permanent recovery (*Osler's Modern Medicine*, v, 635). Exception must be made of the puerperal cases. One such was included in the five reported in 1890. (*Medical News*, October, 1890). This woman made a complete recovery, and she has remained well since. The diagnosis as one of pernicious anemia was at least doubtful, and was so regarded at the time; the subsequent history renders it probable that the anemia was due to toxemia caused by the unsanitary conditions of the house in which she was then living.

This case affords a striking illustration, in the first place, of the uncertainty of the course and duration of pernicious anemia, and in the second place, of the certainty of the final ending, if the sufferer in the meantime does not succumb to some intercurrent affection. In a number of cases the toxemia and prostration are so great at some period of their history that death has been daily expected, and yet, without apparent cause, they have improved and become able to be about in a few days, after which improvement has often been rapid and they have been able to resume their usual occupations. In the case of a stone mason some years ago, the prostration was so great that he was unconscious, blood-stained saliva flowed freely from the mouth, coloring the pillow, and neither food nor liquid could be given. He was, in fact, apparently *in extremis.* Yet a day later he became conscious, took food, sat up, and in two more days travelled one hundred miles to his home. He resumed his work in a few weeks, and spent an active summer. He failed again gradually during the ensuing winter, and died in the spring. The designation given by Biermer of *progressive pernicious anemia* is quite inappropriate, as the disease is nearly always remittent and not progressive, in many the remission being marked and of long duration.

In addition to the irregularity in its progress, the course of the disease presents the greatest variations in symptoms. In some, and these are the most numerous cases, the digestive tract shows marked and frequent disturbance, with vomiting and diarrhœa. The stools are usually watery, and may be offensive, owing to copious secretion into the intestine and vigorous peristalisis. The mouth, as a rule, is healthy. In some cases there is from time to time troublesome superficial glossitis, but in none of my cases have there been the septic gums met with so often by Hunter and regarded by him as the source of the infection, which causes the disease, or, as he believes, one variety of it. In the case of Dr. P. the teeth had been removed some years before the symptoms began, and the gums were quite healthy. Well-fitting false teeth had been worn.

Signs of local disease may be slight or absent. A fair percentage of cases show early and marked symptoms of degeneration in the nervous system, any part of which may be affected. The peripheral

nerves most frequently suffer, as shown by local paresthesia, anesthesia, and trophic changes, especially in the skin, which not rarely presents a glossy surface and other signs of atrophy. The spinal cord is frequently affected, especially in the posterior columns, hence some ataxia. The altered sensations and anesthesia may also be due to cord changes. In a few cases the brain suffers, as shown by well-marked mental disturbance which may persist even when the patient's general condition has greatly improved. A few years ago, in the case of a physician, mental symptoms occurred early and persisted in varying degrees, even when he had improved so much that the blood contained nearly 5,000,000 red blood corpuscles per cubic millimeter and they were of nearly normal appearance.

As to the benefit of arsenic in pernicious anemia, opinions vary. By many it is regarded as of great importance, almost as a specific; by others, an increasing number, it is looked upon as having possibly a little influence on the progress of some cases, but that it is of no benefit in the majority. Arsenic is supposed to act as a stimulant to the blood-forming tissues increasing the production of red corpuscles. Gunn (*Brit. Med. Jour.*, 1908, ii) ascribes to it the effect of rendering the stroma of the red corpuscles more resistant to destructive agencies. It has appeared to me to be in the more acute cases, if in any, that arsenic has a beneficial effect. In these there are the symptoms of an acute toxemia, such as fever, vomiting, diarrhœa, and often delirium. These cases not rarely bear arsenic well, as soon as the vomiting and diarrhœa have ceased, and improvement is often rapid. In such cases the symptoms are chiefly, if not altogether, due to the toxemia. In the more chronic cases with progressive symptoms, often without any acute irritative attacks, but running a slow downward course, arsenic seldom has any beneficial influence; on the contrary, it often causes stomatitis and gastroenteric disturbance. In these cases the symptoms are possibly largely, if not chiefly, due to the secondary degenerative changes in the bone marrow and in the mucous membrane of the digestive tract. Such would seem to be true in Dr. P.'s case at all events. In the first illness, which was acute, arsenic was well borne and the recovery was rapid, not necessarily because of the arsenic; in the second illness, even small doses of arsenic could not be given without

causing stomatitis and epigastric distress. As an evidence of the beneficial effect of arsenic, it is said that those to whom it is given show a larger proportion of remissions than those do who are not so treated. But then these latter cases are usually those who cannot bear it, and include the majority of the worst cases, so that a comparison is misleading.

Many other plans of treatment have been recommended. Red bone marrow is used by Sir Thomas Fraser, and in some cases good results have followed its administration. Various sera have been used subcutaneously, also physiological salt solution. Antiseptics have been given, especially in cases with vomiting and diarrhœa; of these, probably the best are bismuth salicylate and bismuth naphtholate. These have proved useful in controlling diarrhœa. Gastric lavage in suitable cases has no doubt been of benefit, as has also colon flushing.

These means of treatment are useful in some cases, but none of them have more than a limited application. In a disease subject to such marked and sudden changes, either for better or worse, it is difficult to estimate the value of any course of treatment.

The outlook in any case is not necessarily unfavorable for the immediate future, even although the condition may be marked by great prostration. The more prolonged and continuous the patient has been on the "down grade," the more unfavorable is apparently the outlook. However, in most cases temporary improvement is the rule. In the large majority of cases reported, few have lived beyond three or four years from the onset. We cannot hope to be much more successful in our treatment until we have discovered the actual cause of the disease.

DISCUSSION.

Dr. Dock: It does not seem very important to a patient who remained well twenty-two years whether one calls it remission or cure. The longest apparent cure I have seen is thirteen years, and the patient is still living. (After the meeting a letter was received describing a recent visit to the patient and reporting continuous and complete health.) The patient was seen in January, 1897. At that time he was aged sixty-five years, a farmer, perfectly well up to a year

before, since which time he had been getting weak and short of breath, so that he was obliged to stop climbing stairs; pale, but not emaciated. The day before the patient was seen he was obliged to remain in bed. He had one attack of bleeding from the nose; otherwise no hemorrhages. For two weeks he had been vomiting bile-stained material. He had the characteristic appearance of a severe case of pernicious anemia and was extremely weak, so that he had no grip. The spleen was slightly enlarged and thick. Physical examination otherwise was negative; examination of the rectum was negative. The hemoglobin was 20 per cent. by Miescher; red blood corpuscles, 600,000; leukocytes, 3000; eosinophiles, 2 per cent. There were characteristic variations in the size and shape of the red cells; 18 megaloblasts and 3 normoblasts were counted to 314 leukocytes. A bad prognosis seemed justifiable, but, in order to seem to do something, Fowler's solution was given. The patient made a steady and rather rapid improvement and has been perfectly well since. After all, such prolonged freedom from recurrence is hardly more remarkable than the tendency that some patients with pernicious anemia have to a progressively bad course from the beginning. The great majority of cases have remissions lasting from one to two or three, or sometimes five years.

Dr. James B. Herrick: I have had one case in which there was an interval of seven years from the first attack before the relapse occurred. I remember when the patient was first seen he was in a desperate condition, and he had only 365,000 red cells. This patient apparently recovered, much to the surprise of all who saw him. He was able to do a full day's work as a carpenter for nearly seven years. Last year he suffered from a severe relapse, when I thought he certainly would die. Two months later, however, he was on the up grade. That is the only case I have seen with such a long interval between the attacks.[1]

Dr. William S. Thayer: I should like to ask Dr. McPhedran the highest blood count in his case. Did the examination of the blood show it to be perfectly normal so far as the size of the corpuscles was concerned?

I have seen but one of these cases. In the fall of 1890 he presented a typical picture of pernicious anemia. The red cells numbered at one time but 800,000, and the symptoms were characteristic. He improved greatly and left the hospital with over 4,000,000 corpuscles; this was in the following spring. He was then lost sight of until the spring of 1895, that is, about four and a half years after his entrance to the hospital. On this occasion he came in complaining of gastric symptoms. There was a palpable mass in the pyloric region, an absence of free hydrochloric acid in the gastric juice, and the diagnosis was made of carcinoma of the stomach. He had over 5,000,000 red cells, the percentage of hemoglobin was slightly lower than that of the corpuscles and the blood, and was quite normal in appearance. The corpuscles were equal in

[1] Since the meeting of the Association the patient died, August, 1910.

size. Recovery appeared to be complete. He left the hospital in a few days, and I have not seen him since.

With regard to the treatment, I am frank to say that I have never seen a case that was not treated with arsenic. I have always felt that the benefit obtained by the use of arsenic was so evident that I have never felt justified in omitting its use.

Dr. Frederick C. Shattuck: I have seen one case and one only, followed by apparent permanent recovery. The symptoms followed confinement. The clinical and blood pictures alike were absolutely typical of pernicious anemia. The latter was passed upon by Dr. R. C. Cabot. Some years after seeing her I was informed by her physician that recovery was prompt and no recurrence had taken place up to that time. Perhaps we must wait seventeen years. Almost every patient I have ever seen has had arsenic, but they all died.

Dr. McPhedran: The reports of benefit from the administration of arsenic are not always reliable, because the cases are subject to such sudden and rapid changes for better or worse. If arsenic is being taken, the improvement is usually attributed to the drug, although it may have been due to the course of the disease, quite unaffected by the arsenic.

THE X-RAY TREATMENT OF STATUS LYMPHATICUS.

WITH INFERENCES DRAWN THEREFROM CONCERNING THE PHYSIOLOGY OF THE THYMUS GLAND.

By B. K. RACHFORD, M.D.

In 1907 Alfred Friedländer[1] reported a case of status lymphaticus with marked enlargement of the thymus and persistent stridor, which he treated successfully by the x-rays. Heinecke (quoted by Friedländer) demonstrated the selective action of the Röntgen rays on lymphoid tissues, including the thymus, and showed that under their action marked changes occurred in these tissues, with a reduction in their size. Friedländer's successful case directed attention to the x-ray treatment of enlarged thymus in connection with status lymphaticus, and led to the successful treatment by this method of a number of other cases. The purpose of this paper is to call attention to two of these cases which came under my direct observation, and to draw therefrom certain inferences concerning the physiology of the thymus gland.[2]

Case I.—John X., born July 2, 1908, birth weight $6\frac{1}{2}$ pounds, was apparently normal for one month, and was then weaned because of indigestion. When one month of age he choked on a calomel and soda powder, became greatly cyanosed, and was prostrated for a number of hours afterward. From this time on his mother noticed that there was great difficulty in keeping his feet warm, and that at times they were blue. About the middle of December, when five

[1] Archives of Pediatrics, July, 1907.

[2] For many of the facts used in this paper I am indebted to the writings of A. S. Warthin, in Osler's System of Medicine, the Transactions of the Association of American Physicians, 1906, and the Archives of Pediatrics, August, 1909, and to Pappenheimer's paper on the Histology of the Thymus Gland, in the Journal of Medical Research, February, 1910.

and one-half months old, he had an afebrile attack of "bronchitis" of the larger tubes, characterized by cough, coarse rales, wheezing, and dyspnœa; this attack lasted one month. In the middle of February he developed another attack of bronchitis, with the same symptoms as in the preceding attack, except that the cough was more violent and spasmodic. This attack continued until, on March 4, his adenoids were removed under chloroform anesthesia, in the hope of relieving these symptoms. Following the operation the child was better for two days, when the whole symptom group recurred; at this time there was marked stridor and dyspnœa, which interfered with his taking food. On April 3 a second and more radical operation was made for the removal of the adenoids and tonsils. Following this operation for two or three days there was a slight improvement in his symptoms, and then his condition grew steadily worse. The cyanosis, stridor, and prostration increased until on April 12 he was brought to Cincinnati with the diagnosis of thymic asthma. I saw him on his arrival, and asked Drs. Forchheimer and Friedländer to see the case with me. We concurred in the opinion that the child had status lymphaticus and was suffering from thymic asthma. The thymus gland, greatly enlarged, was readily mapped out by percussion. A blood examination by Friedländer showed a chloro-anemia and a well-marked lymphocytosis. The patient was pale, fat, and flabby. He suffered constantly from stridor, so severe that it was almost impossible for him to take food. He also had a severe paroxysmal cough, which came on at short intervals and increased the stridor into an attack of asthma associated with such great cyanosis that his life was threatened. The child was held the greater portion of the time stomach down, across the mother's lap; in this position the stridor was less severe. The lymphatic glands were increased in size, the spleen was slightly enlarged, and, as previously noted, the adenoids and tonsils had been removed. The tuberculin skin test was negative.

So urgent were the symptoms that the *x*-ray treatment was begun on the day of his arrival in Cincinnati, April 12, 1909. At each treatment the rays were applied both anteriorly and posteriorly over the region of the thymus. The rest of the body was carefully guarded from their influence. Sixteen treatments in all were given,

extending over a period of six weeks. In the beginning the time of exposure to the rays was three minutes anteriorly and three minutes posteriorly. In the later treatments the exposure was eight minutes. The treatment was interrupted during the fourth week.

Within forty-eight hours after beginning the treatment there was slight improvement in the symptoms, especially the stridor, and this improvement continued steadily throughout the eight weeks he was under treatment. During this time the thymus gland was reduced to its normal size, and the dulness posteriorly on the left under the angle of the scapula, which we thought to be due to lymphatic enlargment and pulmonary compression, also disappeared. The paroxysmal cough and stridor had been almost entirely relieved and the child had gained steadily in weight and strength, but he still appeared anemic. On May 17 he was taken to his home in Kentucky, and within two weeks thereafter his father, who is a physician, reported that the cough and stridor had entirely disappeared, and that the child was apparently well. From the time the child returned home until the present time, April 11, 1910, he has had, at intervals of about three months, three very slight attacks characterized by cough and dyspnœa, which occurred without apparent cause and which were promptly relieved by one or two mild *x*-ray treatments. Apart from this, he has presented the appearance of a sturdy infant developing along normal lines. His father wrote me on April 11: "It will be just one year ago tomorrow since I took my baby to see you, and he now seems to be perfectly well. About three months ago he had another slight recurrence, which yielded promptly to two mild exposures to the *x*-rays. It seems that he may from time to time need an occasional treatment, but I shall remember your advice and not expose him to the rays unless there seems real occasion for it."

Case II.—John Y., born July, 1908. When about six months of age it was noted that he had rapid heart action and difficulty in breathing from slight causes. From this time on these symptoms gradually increased in severity and the general symptom complex of status lymphaticus slowly became apparent. On November 1, 1909, I saw the patient for the first time with Dr. Sam Rothenberg, and from this time on the case was cared for jointly by Dr. Rothenberg and myself. On this date the child was fifteen and one-half months old

and presented well-marked and aggravated symptoms of status lymphaticus, which Dr. Rothenberg informed me had existed for some months. He was fat, flabby, anemic, and markedly lacking in physical development, especially his lower extremities. He had great dyspnœa, with well-marked stridor, which at times during the past few months was greatly aggravated by such slight causes as fits of anger, indigestion, and catarrhal conditions of the throat and nose. The child at times had a spasmodic cough, which would aggravate the stridor and produce cyanosis. The heart was dilated and its muscle weak and irritable. The action of the heart was rapid at all times, and this rapidity was greatly increased by the same causes which aggravated the stridor. The spleen, lymph nodes, and tonsils were enlarged, and there was a marked itching of the skin of the face and head, which caused the child to mutilate the skin of these regions by scratching. A well-marked enlargement of the thymus was demonstrated by percussion, and a blood examination by Dr. Max Dreyfoos demonstrated a very pronounced chloro-anemia and well-marked lymphocytosis. The blood examination was as follows: Hemoglobin, 65 to 70 per cent.; red corpuscles, fresh preparation, showed considerable poikilocytosis, a few "ameboid" micropoikilocytes, and on the whole the red cells were smaller than normal; the stained preparation showed 6 normoblasts to 500 whites counted; white corpuscles, 24,600; red corpuscles, 5,881,250; color index, 0.58; differential count, polymorphonuclear neutrophiles, 25.60; small lymphocytes, 61.80; large lymphocytes, 2.60; large mononuclear leukocytes, 8.40; eosinophiles, 0.60; mast cells, 1.00.

The patient was immediately referred to Dr. Sidney Lang for *x*-ray treatment. In all, twelve treatments were given during the next six weeks, and during this time the symptoms of status lymphaticus gradually improved. There was an early and marked diminution in the size of the thymus and marked improvement in the stridor and heart action; the spleen and lymph nodes grew smaller and the itching of the skin largely disappeared, but the child still presented a very anemic appearance. A blood examination on December 26, 1909, showed that the lymphocytosis had disappeared, but that the chloro-anemia was slightly more aggravated than before. The blood state at this time was as follows: Hemoglobin, 50 to 55 per cent.; fresh

preparation, reds pale and smaller than normal; considerable poikilocytosis and anisocytosis; stained preparation polychromatophilia; 2 nucleated reds to 300 whites counted; white corpuscles, 6800; red corpuscles, 4,675,000; color index, 0.56; differential count, polymorphonuclears, 38.00; small lymphocytes, 46.00; large lymphocytes, 6.00; large mononuclear leukocytes, 7.67; eosinophiles, 1.66; mast cells, 0.67.

Following the above blood examination the *x*-ray treatment was discontinued and the child was given citrate of iron hypodermically. He continued to improve in general health, and the slight amount of dyspnœa, which still appeared at times, continued to grow less. The heart was gradually reduced in size and its action became more normal. This improvement continued until January 12, when the child was taken ill with bronchopneumonia, from which he made a rapid recovery. February 27, a blood examination was made, with the following results: Hemoglobin, 90 per cent.; fresh preparation, reds smaller than normal; moderate poikilocytosis; considerable anisocytosis; rouleaux formation fairly well marked; white corpuscles, 14,500; red corpuscles, 5,906,250; differential count, polymorphonuclears, 69.25; small lymphocytes, 22.50; large lymphocytes, 3.25; large monuclears, 3.25; eosinophiles, 1.50; mast cells, 0.25.

It will be noted that the special point of interest in the above blood picture is the appearance of a polymorphonuclear leukocytosis, while the lymphocyte count remains low. It was suggested by Dr. Dreyfoos that this might be due to a slight influenza which the baby had at the time, and which had developed after Dr. Rothenberg and I had seen the baby and asked for the blood count on February 20. In this connection, however, it may be interesting to note that Rudberg, quoted by Pappenheimer, notes in his study of the regeneration of the thymus in rabbits following Röntgenization, that during the later stages of this regeneration there is a marked invasion of the thymus gland with polynuclear leukocytes derived from the blood. This would indicate that a polynuclear leukocytosis might be a physiological reaction following the *x*-ray treatment of the thymus. Without other treatment than fresh air and careful feeding this child continued to improve in general health, until on April 5, 1910, he presented the appearance of a normal child. The dilated heart had

returned almost to normal size and none of the symptoms of the status lymphaticus were present. The child at this time was gaining in weight and developing along normal lines, and the blood state below given is almost, if not quite, normal; Hemoglobin, 75 to 80 per cent.; fresh preparation, red corpuscles slightly under normal size; small number of poikilocytes; white corpuscles, 9800; red corpuscles, 4,881,250; color index, 0.9; differential count, polymorphonuclears, 48.33; small lymphocytes, 39.67; large lymphocytes, 2.66; large mononuclear leukocytes, 3.67; eosinophiles, 5.33; mast cells, 0.34.

A study of this case indicates that the disappearance of the lymphocytosis under the *x*-ray treatment of the thymus gland in the status lymphaticus is so marked that a careful study of the blood state in this condition will give important information not only as to the efficacy of the treatment, but as to the length of time this treatment should be continued. It will perhaps be wise to discontinue treatment when the lymphocytosis disappears, even though there still be left some cough and stridor. The chloro-anemia, which is not improved under the *x*-ray treatment, may be aggravated if it be continued too long. Following the *x*-ray treatment in these cases, hypodermic injections of iron, with careful feeding and fresh air, may be necessary to restore the blood state to a normal condition. In both of the cases here reported slight cough and stridor were present when the *x*-ray treatments were discontinued, but disappeared entirely a few weeks later.

Physiology of the Thymus. The histology of the thymus gland is very fully discussed in a paper by Pappenheimer in the *Journal of Medical Research*, February, 1910. From this paper it appears that while many points concerning the development and histology of this gland are still in dispute, it is rather generally conceded that it is relatively large in infancy and early childhood, but that it gradually increases in size up to the fifteenth year of life, and thereafter regressive changes slowly take place which diminish its physiological efficacy. It is also very generally believed that the thymus furnishes an internal secretion which exerts an important influence on nutritional processes, and that its period of greatest functional activity along this line is during fetal life and early childhood; this function falls off most rapidly after the fifteenth year, but probably remains more or less

active throughout life. For a review of the various inferences and suggestions which have been made concerning the physiological functions of this gland the reader is referred to the papers by Warthin, previously noted.

It is my purpose here to call attention to the following facts which I believe have been demonstrated by the *x*-ray treatment of the enlarged thymus gland in the condition known as status lymphaticus, and based upon these facts I shall offer an hypothesis concerning the functions of this gland, which, if true, will have an important bearing upon the pathology of this disease.

In the *x*-ray treatment of the status lymphaticus in infants and young children, although no portion of the body is exposed to the influence of the rays except that which directly holds the thymus gland, we have as a result of this treatment:

1. Decrease in size of the hyperplastic thymus, with the disappearance of the cough, stridor, and asthma.

2. Decrease in size of the enlarged spleen and lymph nodes.

3. The exhaustion and general feebleness of constitution give place to normal conditions of health and strength, and physical and intellectual growth are greatly stimulated.

4. A rapid disappearance of the marked lymphocytosis, which characterizes this disease.

5. Excessive physiological action of the thymus gland is controlled. (The slight return of the symptoms, stridor, cough, etc., at intervals of three or four months in one of my cases, and the quick control of these symptoms by one or two exposures to the *x*-rays, indicate that the gradual regeneration of the thymus following the *x*-ray treatment may be accompanied by a gradual reproduction of the same pathological conditions, hypersecretion, etc., which were present before the treatment was begun.)

Since the above remarkable results are brought about by the action of the *x*-rays on the thymus gland, it would appear that the excessive physiological activity of the thymus gland bears the same relationship to the status lymphaticus that excessive activity of the thyroid gland bears to exopthalmic goitre. One seems justified in inferring from the above facts that the exciting cause of true status lymphaticus acts primarily on the thymus gland, commonly producing marked hyperplasia of this organ with an increase in or perversion of

its internal secretion, and that this increased or perverted secretion is responsible for the general hyperplasia of lymphoid tissues, the lymphocytosis, and general feebleness of constitution which occur in this disease. This inference seems justified by the facts above noted, that the general hyperplasia of lymphoid structures, as well as all of the other symptoms of status lymphaticus, disappear when the x-rays reduce the thymus to normal size and, perhaps of more importance, to normal functional activity.

If the above hypothesis be true, that under pathological conditions an excess or perversion of the internal secretion of the thymus may produce hyperplasia of the thymus gland itself and of lymphoid tissues in general throughout the body, the inference seems plain that the normal thymus gland, which is at the height of its functional development in intra-uterine and early extra-uterine life, exercises a preponderating or controlling influence over the lymphoid tissues of the body, their functional capacity being increased or diminished by the increase or diminution of the internal secretion of the thymus. This hypothesis is in accord with the increased activity of lymphoid tissues during early life, and with the gradually diminishing activity of these tissues in later life, as the physiological atrophy of the thymus gland gradually diminishes its internal secretion.

The hypothesis that the thymus gland during infancy exercises an influence over the functions of lymphoid tissues explains many of the observations which have been made in connection with this gland.

Up to the present time, according to Warthin, seven cases of enlarged thymus producing thymic asthma have been cured by the partial or complete removal of the enlarged gland. One of these cases operated by König was an infant only nine weeks old. Complete relief from the symptoms followed the operation, but König subsequently advised against complete thymectomy in these cases, because the case operated on by him afterward, developed rickets and did not walk until after it was four years of age. It will be noted that this case was operated upon at the very time in the life of the infant when the thymus gland is most active, and the infant was thereby deprived during the first and second year of its life of the physiological function of this organ, and thereby suffered profound nutritional disturbances.

The experiments of Basch, to the effect that extirpation of the thymus in "young" dogs is followed by lack of bony development and serious nutritional disturbances, is in accord with König's observations. Stokes, Ruhräh, Rohrer, Dudgeon, Bovaird, Nicholl, and many others have noted the fact that primary marasmus is associated with thymic atrophy. Warthin says that in primary marasmus thymic atrophy appears to be constant, and that similar changes also occur in the spleen and lymph glands, "suggesting a general lymphoid exhaustion." In these cases it would appear that the thymic atrophy is the initial lesion and one of the causative factors in the production of infantile marasmus. This condition would naturally occur if by destroying the functional activity of the thymus a "general lymphoid exhaustion," or general functional debility of all the lymphatic tissues resulted in conformity with the hypothesis above outlined.

Warthin says that "in true acephalic monsters the thymus may be entirely absent; and up to the present time such cases are the only ones in which a total absence of the organ has been definitely shown to exist." These facts apparently indicate that there is some relationship between the absence of the thymus and the lack of development here referred to. If this be true, it points to the conclusion that the thymus gland during intra-uterine life exercises, by means of some internal secretion, a powerful influence over the metabolic processes which are necessary to the normal development of the fetus. This conclusion is in accord with the hypothesis that the thymus gland exercises a controlling influence over the development and functional activity of lymphoid tissues.

Svehla[1] prepared fresh and dried thymus glands and fed them to dogs with the following results: (1) Drop in blood pressure, as result of weakness and paralysis of vasoconstrictors. (2) Acceleration of pulse due to action of toxin on heart. (3) Large doses produced death of animals, with restlessness, collapse, and dyspnœa, and postmortem showed death from suffocation.

Sachsa[2] injected a 10 per cent. watery solution into curral veins, and produced a fall in blood pressure, acceleration of the pulse, and death from acute suffocation. This toxic action was more marked

[1] Wien. Med. Blatt., 1896.

[2] Centralbl f. Allg. Path. u. path. Anat., 1897.

in young animals. Both Svehla's and Sachsa's conclusions, that thymic asthma and thymic death may be due to hyperthymization of the blood, are in accord with my hypothesis.

On finishing this paper there came to my notice the research of Lucien and Parisot.[1] These observers made a careful study of the influence of thymectomy in rabbits, and found that in very young animals removal of the thymus was followed by a noticeable retardation of growth. The changes in the skeleton were in the weight and general dimensions of bones; no curvatures, epiphyseal enlargements, or bony softenings were found. The testicles and ovaries were diminished in size, corresponding with the lack of development of the organism in general. All of these changes were less noticeable in older animals, and did not occur at all in animals that had attained their full development. These findings of Lucien and Parisot may be explained by the hypothesis above advanced.

[1] Archives de Médecine Expérimentale et d'Anatomie Pathologique, January, 1910.

CONGENITAL SYPHILIS OF THE HEART.

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The purpose of this paper is to show that there exists an especial form of interstitial myocarditis, localized or diffuse, due to the presence of the *spirocheta pallida*, and resulting from congenital infection. This form of myocarditis may exist independently of any other signs or symptoms of congenital syphilis—in fact, it may be the only pathological condition attributable to syphilis that can be demonstrated at autopsy in the body of the patient; or other lesions of congenital syphilis may be associated with it. Secondly, this form of syphilitic disease of the heart is an important cause of asphyxia neonatorum and unexplained sudden death in early life; and some of the cases prove that it may cause cardiac weakness in childhood and youth, forming an anlage upon which subsequent infections (streptococcus particularly) produce valvular lesions. Further, the condition may be associated with infantilism, hypoplastic constitution, or less severe grades of underdevelopment. Finally, it may lead also to the production later in life of fibroid heart and coronary sclerosis, with the complications and sequelæ incident to these conditions. The material upon which these conclusions are based consisted of autopsy material of 12 cases furnished in part by the clinics of the University Hospitals, and in part from the private practice of Ann Arbor and Detroit colleagues. Without giving a detailed description of each of these cases, they may be divided into three groups according to the age of the patient: (1) Cases occurring in infancy, (2) in childhood, and (3) after the age of puberty. Three-fourths of the cases fall into the first two classes—infancy and early childhood. Of these

9 cases, only 1 had been diagnosticated as congenital syphilis before death. The others all came to autopsy, that the problem of an undiagnosticated condition and unexplained death might be solved. Of the 3 cases occurring after the age of puberty (ages fifteen, eighteen, and twenty-two years), all had an old history of cardiac disease, and all showed decided underdevelopment, one, a girl, aged eighteen years, presenting a marked condition of infantilism. The oldest case was a young woman student giving a history of having been a "blue baby," and having from birth suffered from cardiac disturbance. Death took place from a streptococcus—endocarditis and septicemia engrafted upon an older interstitial myocarditis. Her father was in the late stages of locomotor ataxia. A clinical history of congenital syphilis was obtained in the other 2 cases after the diagnosis had been made pathologically.

My share in these cases having been wholly from the pathological side, it is not necessary to go further into the clinical history than the main points given above, which may be briefly stated as follows: Only in the older cases was there a definite history of cardiac affection, and in none of the cases was syphilis considered by the clinician as having anything to do with the clinical symptoms and termination of the case. Only in one case was congenital syphilis positively diagnosticated clinically, and in this case no affection of the heart was suspected, although at autopsy this organ showed the most severe interstitial myocarditis, with the greatest number of spirochetes present, of all the cases. For the sake of brevity the pathological conditions may be summed up as follows:

1. *Gross Appearances.* In the majority of the early cases the heart was large and dilated; in the others, normal in size or even undersized. The heart muscle was usually pale or contained lighter areas. The walls were usually thicker than normal, the right ventricular wall in some cases being as thick as the left, justifying a diagnosis of hypertrophy from the gross appearances. The muscle seemed moister, softer, and more translucent than normal. In other hearts, aside from a dilatation of the cavities, nothing pathological was noted in the gross examination, and the condition was not discovered until microscopic examination was made.

Localized patches of interstitial myocarditis can exist without causing notable changes in the gross appearances. In the older cases there was in all the gross picture of a mitral endocarditis, with insufficiency, compensatory hypertrophy, and dilatation. Nothing in the gross appearances indicated the existence of a syphilitic myocarditis, and this condition was not discovered until the microscopic examination.

2. *Microscopic Appearances.* The common feature of all of these cases is the occurrence throughout the myocardium of numerous or few light-staining patches (hematoxylin and eosin or Van Gieson's) separating or replacing the muscle fibers, and made up of a fibroblastic or myxomatous tissue, having a delicate granular or fibrillar reticulum in which lie numerous cells of lymphocyte or plasma-cell type, as well as numerous large epithelioid cells with abundant pink-staining granular protoplasm and pale nuclei. The latter type of cells presents the greatest variety of size and form, round, oval, spindle, branched, etc. Many of these cells are vacuolated, and fragmentation with loss of nucleus is a common feature of the larger patches. The infiltration of plasma cells and cells of the large lymphocyte type is often so marked as to catch the eye at once as a focus of small-celled infiltration. The most characteristic feature of all of these cases, however, is the light-staining, fibroblastic tissue containing peculiar degenerating cells of fibroblastic or epithelioid type. The characteristics of this interstitial process are so marked and differ so much from ordinary interstitial processes that when its peculiarities are once recognized it is identified with ease.

The process does not seem to be confined to any one part of the heart wall. It may be diffuse, occurring in nearly every section taken; in other cases many blocks may be cut before a patch is found. In some cases the left ventricular wall, or the septum may show the most numerous patches, but in the newborn the wall of the right ventricle usually showed the most marked changes. Some blocks show the process to be most marked beneath the epicardium, others show it localized beneath the endocardium. On the whole, the process seems to be more frequently localized near the epicardial surface. A striking feature of the patches

is their tendency to run in narrow or broader bands between the muscle fibers. These bands may be of the width of 5-20 muscle fibers. Rarely are they large enough to be seen with the naked eye. From the larger bands smaller strands invade the neighboring muscle separating the fibrils. In sections of muscle cut transversely occasional broad bands of the light interstitial tissue cross the field. Occasionally, larger areas of a more diffuse process are found, the muscle fibrils appearing smaller than normal and separated by narrow strands of fine reticulum containing the large epithelioid cells, so different in size and staining and amount of cell body from the normal stroma of the heart wall.

The interstitial process seems to follow the smaller arterioles and capillaries. It is abundant also about the medium-sized vessels, less so about the larger ones, although perivascular collections of lymphocytes and plasma cells are numerous about these. The smaller vessels show an epithelioid proliferation of their walls, and the lumina are often wholly filled with cells of the same type as those of the stroma. The larger vessels, both arteries and veins, show varying degrees of thickening, the intima and the adventitia showing most prominently the result of cellular proliferation. Even in some of the newborn cases the adventitia of some of the larger vessels was markedly increased and distinctly fibroid in character. Obliterating endarteritis, however, was not the common or most characteristic feature of these congenital cases, and in that respect the condition differs also from the common variety of acquired syphilis of the heart seen in adults. The most prominent feature of all of these cases is the *fibroblastic or epithelioid proliferations of the stroma along the course of the smallest vessels and apparently arising from their walls or the perivascular tissue.*

Another striking feature of the process, as shown in all cases, is the condition of the heart-muscle fibrils. Those show in the immediate neighborhood of the fibroblastic proliferations a peculiar pale coagulation-degeneration or necrosis, the protoplasm losing its striations and its ability to take the eosin stain, while the nuclei are larger, swollen, and stain but lightly with hematoxylin. In the areas where the intermuscular proliferation is most marked and the fibrils most widely separated, bundles of pale atrophic fibrils

are occasionally seen, the protoplasm of which will no longer take the eosin; and it is almost impossible to distinguish the fibrils from the surrounding epithelioid tissue except by their form and branching. Such fibrils appear to be gelatinous or partially liquefied. They still contain large, pale-staining nuclei, and there is an apparent increase of the latter. This point could not be definitely determined, as in these sections it was practically impossible to tell whether the nuclei belonged to the fibrils or to the epithelioid tissue, and in thicker sections the difficulty of judgment was even greater. Fat vacuoles were common throughout the degenerated fibrils.

It must not be forgotten that in some hearts the intermuscular proliferations of the stroma are not so striking on first sight, but that to the casual observer they might be interpreted simply as an "increase of stroma," "edema," etc., without any suspicion of their syphilitic nature being aroused. Indeed, it was only the discovery that such soft, cellular, semifluid portions of the cardiac stroma *contained spirochetes in great numbers* that first led to their recognition as syphilitic, and furnished me, at least, with a criterion, on the basis of which I now unhesitatingly class such changes in the heart as syphilitic beyond any question.

In all of my cases the interstitial changes outweighed in prominence the vascular ones; indeed, in some of the early cases evidences of endarteritis could be found only after some search. The older the case, the greater the involvement of the large and medium-sized bloodvessels, and the greater the frequency of occurrence of fibroid patches about the vessels or in the heart muscle. In the oldest case the soft, fibroblastic areas were found, just like those in the younger hearts, and it was from such interstitial formations that the suspicion of congenital syphilis was first entertained. The occurrence of fibroid patches in the older cases in association with the fibroblastic areas and more marked vascular areas points to an age relationship between the two conditions, although the fibroid areas may have been the result of an anemic infarction due to the obliteration of the arteries, rather than as the result of a fibroid transformation of the fibroblastic tissues. *No gumma formation* was found in any of these cases, and the process is not

identical with the gummatous myocarditis seen in late acquired syphilis. It is characterized by a much less lymphocyte and plasma-cell infiltration, and is irregularly diffuse rather than circumscribed, and there is no central caseation. Giant cells were never found. There is also no new formation of bloodvessels containing blood, although it is possible that the fibroblastic areas may be largely made up of cells derived from the proliferating vessel walls.

Besides the peculiar pale degeneration of the muscle fibrils described above, larger areas of vacuolated muscle fibers occur in the neighborhood of the larger bloodvessels. These vacuoles give the fat reaction with Sudan III and Scharlach R. In some of the newborn hearts this fatty degeneration of the heart muscle was so extensive as to account in part for the pale color and greater translucency of the heart wall. Cellular infiltration and fibroblastic proliferation were, as a rule, absent from these areas of fatty muscle. As described above, the muscle fibrils of the areas of interstitial change showed the pale degeneration with loss of staining power and striation, rather than this more marked fatty change, although often containing numerous small vacuoles.

Localized fibroblastic proliferations of the endocardium were occasionally found, the new tissue showing the same characteristics as that of the intermuscular areas. Beneath the epicardium small areas of lymphocyte- and plasma-cell infiltration were common in the more severe cases, and in such areas the epithelioid proliferation was not as marked as between the muscle fibrils. Fibroid thickenings (sclerotic patches) were found on both epicardium and endocardium of the older cases. Here again an age relationship is possible, but cannot be determined positively.

Of the other organs of these cases the liver and spleen most frequently showed evidences of congenital syphilis in the form of the characteristic intralobular increase of the reticulum in the liver, and the diffuse reticular hyperplasia of the spleen. One very important point established was the occurrence of the syphilitic changes in the heart, as described above, in the absence of lesions of congenital syphilis elsewhere. Another feature of some importance is the occurrence of numerous hyaline glomerular scars in the kidneys of these cases. I have long looked upon the occurrence

of hyaline glomeruli in the kidneys of infants as an important sign of congenital infection or intoxication—usually syphilitic. It has been a common finding in all cases of congenital syphilis the kidneys of which I have examined. Syphilitic changes in the wall of the aorta and larger arteries were also found and will be reported in another article.

The proof of the syphilitic character of this form of interstitial myocarditis rested upon two points—the co-existence of typical syphilitic liver, or upon the demonstration of the presence of spirochetes. Levaditi's method was employed for this purpose. In sections so treated the fibroblastic epithelioid areas of the heart wall were found to be crowded with spirochetes. They lay at every possible angle and in every direction in the soft semifluid intercellular substance, and between and upon the muscle fibrils, and in the case of the very pale degenerated fibers apparently within the substance of the fibril. In the young hearts the parasites stood out sharply and clearly revealed their distinguishing characteristics. Their number was often surprising. Every section would show great numbers cut at all planes and angles. Wherever the fibroblastic areas were present spirochetes were always present, usually in very large numbers. They were always more easily demonstrable in heart muscle than in liver or spleen, the coarser reticulum in the latter organs obscuring the picture more or less. For the demonstration of spirochetes within tissue I know of no material so valuable for class work as congenital syphilis of the heart.

In the portions of the heart wall away from the areas of proliferation and pale degeneration of the muscle occasional spirochetes are found in the tissue spaces, but never so abundantly as in the pathological areas. Within the bloodvessels they are frequent. Their infrequency also in the areas of marked fatty degeneration around the larger vessels makes it the more probable that this change is due to localized circulatory disturbances rather than to the localization of the spirochetes. One very important finding was the localization of spirochetes in the heart when they could not be found elsewhere.

Summing up the findings in these cases, we must conclude that

there exists not infrequently a characteristic form of interstitial myocarditis due to the localization of colonies of the spirocheta pallida, the infection being congenital in its origin. Turning to the literature on syphilis we find everywhere the statement that congenital syphilis of the heart is rare. It is only recently that the important role played by acquired syphilis in the production of cardiac disease in the adult is becoming recognized. The writers of the generation just passing away, with but few exceptions (Semola, Sacharjin, etc.), considered syphilis of the heart as rare.

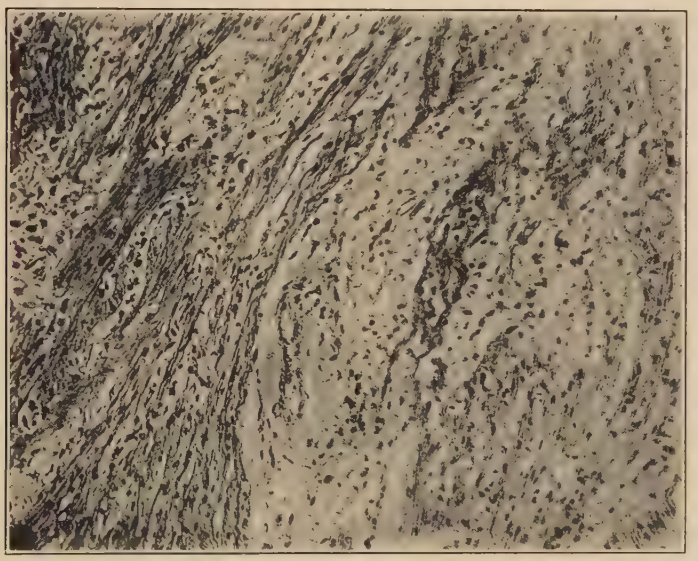

Fig. 1.—Congenital syphilis of the heart. Sudden death second week after birth. Areas of interstitial myocarditis. (Low power.)

Within recent years this view has changed so rapidly that the statement is now made that at least one-tenth up to one-third or more of all cases of heart disease are due to syphilis. In this change of view congenital syphilis has not been included, and the most recent chapters upon the subject still insist upon the rarity of congenital syphilis. These conclusions are based largely upon the study of heart syphilis made by Mracek in 1893.

Of the 112 cases of heart syphilis collected by Mracek, only 9 were regarded as congenital; and as Hektoen has already pointed

FIG. 2.—Diffuse interstitial fibroblastic proliferation. Congenital cardiac syphilis. (Higher power view.)

FIG. 3.—Congenital cardiac syphilis. Perivascular fibroblastic proliferation. Neighboring heart muscle (upper left) shows marked fatty degeneration (vacuolation).

FIG. 4.—Perivascular fibroid thickening and proliferation. Marked fatty degeneration of muscle. Congenital syphilis. (Low power.)

FIG. 5.—Spirochetes in area of fibroblastic proliferation. Congenital cardiac syphilis. The numerous black dots and lines represent portions of spirochetes. (About 1000+.)

out, the syphilitic nature of some of these is doubtful. In 1 case, however, that of Coupland, the condition was evidently that of a diffuse interstitial myocarditis. In 150 autopsy examinations of congenital syphilis studied by Mracek only 4 cases of cardiac syphilitic affection were found, 2 representing a nodular or gummatous form, the other 2 a more acute, diffuse, interstitial type of myocarditis. Since Mracek's study the number of reported cases of congenital cardiac syphilis has not been greatly increased. Hektoen, in 1896, reported a case of focal interstitial myocarditis in an infant, aged six weeks. The description of the intermuscular infiltration suggests strongly the same type of myocarditis as described above, but the nodular or gummatous character was marked enough to justify him in regarding it as a gummatous myocarditis due to congenital lues. Hektoen takes occasion to point out the dangerous nature of congenital syphilitic myocarditis as a possible cause of sudden death in apparently healthy children, and concludes that the lesion has a clinical and practical interest of much greater weight than the interest previously accorded it as a pathological curiosity. In 1897 Guggenheimer described a rare case of fatty degeneration of the heart in a syphilitic newborn. He regarded it as a rare form of syphilitic myocarditis, different in type from the gummatous or fibroid forms. In 1898 Le Count reported a case of "gumma" of the heart in the newborn. His description of the microscopic findings agrees with that of my cases, and the condition is apparently the same, the white area seen being a large patch of diffuse interstitial myocarditis without true gumma formation.

In 1898 Adler, before this Association, made the most important contribution to the knowledge of congenital syphilis that has yet been given. Adler examined the hearts of 4 syphilitic infants, without any symptoms of cardiac disease, and dying of acute enteritis. To the naked eye the hearts appeared perfectly normal. In 2 of the cases he was unable to discover any changes that could be attributed to syphilis. In the other 2 hearts he found lesions regarded by him as undoubtedly syphilitic. One of these hearts showed only a localized patch of proliferating endarteritis in a small branch of the left coronary artery, at the point of greatest develop-

FIG. 6.—Congenital cardiac syphilis. Spirochetes in area of intermuscular fibroblastic proliferation. (About 1500+.)

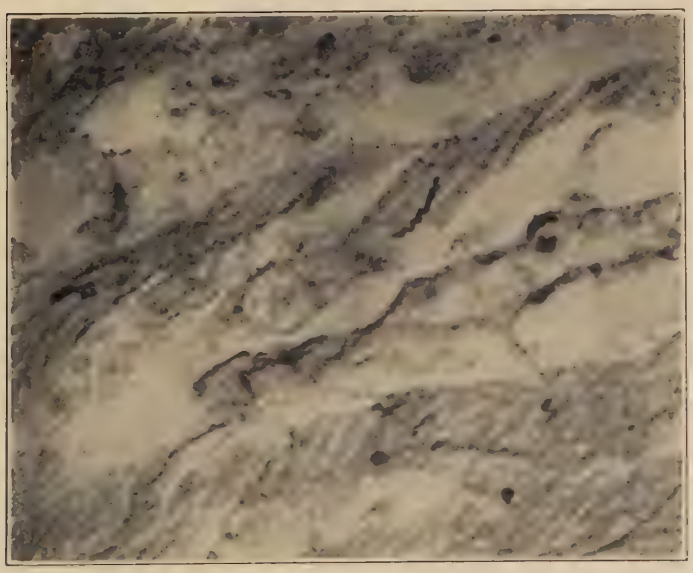

FIG. 7.—Congenital cardiac syphilis. Spirochete in or upon muscle fibril showing pale degeneration. (About 1500+.)

ment almost occluding the vessel, and in the immediate neighborhood of the vessel a minute area in which the muscle fibrils were more widely separated than normal and the intermuscular spaces infiltrated with cells. The other heart showed a condition that, from the description given and from his Plates II, III, and IV, is surely identical with the form of interstitial myocarditis seen in my cases. This heart was from a male child, aged three and a half months, dying from intestinal catarrh and bronchopneumonia. The intermuscular proliferations described by Adler as occurring in this case are of the same type as in my cases; he noted the same degenerative changes in the muscles, and the fact that the lesions were most abundant near the epicardium. In both of these cases Adler's criterion for the diagnosis of syphilis was based upon the vascular changes, particularly the endarteritis He regarded the intermuscular condition, however, as representing a very early state of interstitial myocarditis. Adler concludes his article by emphasizing the necessity of methodically considering syphilis as an etiological factor in heart disease.

From these few observations of congenital syphilis of the heart found in the literature, it is easily understood why all the textbooks consider it to be rare. It must be borne in mind, however, that the old criterion of diagnosis of heart syphilis depended upon the finding of a gumma in the heart. What is really the case is the fact that *gumma of the heart is rare in congenital syphilis, but that congenital syphilis of the heart in the form of a localized or diffuse interstitial myocarditis is most probably not rare. The new criterion is the demonstration of the spirocheta pallida in the proliferating interstitial tissues of the heart wall.* Adler could base his diagnosis of syphilis only upon the endarteritis. I have shown that the same type of interstitial myocarditis in the absence of coronary endarteritis is syphilitic, by demonstrating that these light-staining patches of proliferating stroma represent localized colonies of the spirochete and that the organism occurs in such patches in extraordinary numbers. The myocarditis described by Coupland, Hektoen, and Le Count I believe to be of the same type, sufficiently localized in the cases reported by the last two writers to be visible to the naked eye and to be interpreted as

FIG. 8.—Congenital syphilis of the heart. Area of proliferation in pericardium.

FIG. 9.—Congenital syphilis of the heart. Area of fibroblastic infiltration in heart muscle.

gummata. It is very probable that this form of congenital cardiac syphilis is not uncommon. As the cases of Adler and mine show, it may exist to a marked degree without causing any macroscopic changes in the heart hitherto regarded as syphilitic. Therefore, in all cases of cardiac disturbance in children, congenital syphilis should be carefully considered as a possible factor.

My series of cases also show that it can be a cause of asphyxia neonatorum and unexplained sudden death in infancy. Under such circumstances the possibility of congenital cardiac syphilis must be borne in mind and a thorough microscopic study of the heart carried out. The same thing is true of cases of non-development, infantilism, chronic valvular lesions in children and young adults, etc. For all of these conditions an etiology of congenital syphilis of the heart is possible, and the diagnostic criterion is the demonstration of fibroblastic areas in the heart wall containing colonies of spirochetes.

The fatty degeneration of the myocardium described by Guggenheimer and believed by him to be due to syphilis, deserves mention here, since all of my cases showed patches of marked fatty change. As suggested by Guggenheimer, it may be the result primarily of the syphilitic infection, or may be caused by it secondarily as a result of a lack of oxygen.

In conclusion, congenital syphilis of the heart occurs most frequently in the form of a diffuse interstitial myocarditis due to the presence of the spirocheta pallida in large numbers, without ordinarily producing characteristic macroscopic changes, so that the absence or presence of congenital cardiac syphilis can be told only by a thorough microscopic examination of the heart wall.

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DISCUSSION.

Dr. Isaac Adler: I merely want to say that the histological findings of Dr. Warthin are practically the same as I found years ago and which I demonstrated to this society. The only difference, however, is that I distinctly found changes not only in the perivascular tissues, but in the vessels themselves; in the typical cases there was a nodular form of syphilitic endarteritis. I had different material to work with than had Dr. Warthin. I had young babies who died of intercurrent diseases, but who had a complete history not only of congenital syphilis, but had also numerous syphilitic lesions. This was before the discovery of the spirocheta pallida, but there was no doubt about these children being syphilitic. I examined four hearts in all. In two of these the lesions described by Dr. Warthin and myself were present. In the other two hearts no lesions whatever were produced. I wish to emphasize this one point, that in my cases at least the lesions were not merely and solely interstitial, but that a very plainly demonstrable nodular syphilitic endarteritis was also present.

Dr. A. S. Warthin: There is one point that I should like to emphasize, the explanation of sudden death in newborn children. In such cases the heart should be examined microscopically; in fact, this should be done in every case in which the cause of the sudden death is not easily explained. I feel quite sure that some of these cases are the result of congenital syphilis and unrecognized. Such an examination will clear up a certain proportion of the cases and solve some of the problems that have interested the pathologists. I believe that a large percentage of such cases will turn out to be syphilitic.

INTRACELLULAR FERMENT ACTION IN DIABETES.

By ALONZO ENGLEBERT TAYLOR,
PHILADELPHIA.

The reactions in the carbohydrate metabolism that are, so far as known, concerned in the question of diabetes are the following:

The combustion of sugar.

The conversion of sugar into glycogen.

The conversion of sugar into fat.

The conversion of d-galactose and d-levulose into d-glucose.

Since it can be shown, chemically, that these are wholly different reactions, we assume that they are the results of entirely different enzymes. That they are all typically enzymic reactions, as they occur within the body, will be recognized by all. There is a large amount of experimental work upon these reactions in the plant and animal world, and it is clear that different ferments are responsible for them, as they occur in the body. To what extent are they modified in diabetes? We are limited here to typical diabetes, the relations of which have, in the main, been made clear by the investigations of the results of the removal of the pancreas in animals.

The last reaction is not altered in diabetes. This reaction occurs largely, if not wholly, in the mucosa of the alimentary tract, and in general it is certain that the diabetic retains the normal power of converting d-galactose and d-levulose into d-glucose. While occasionally it may seem, for a few days, that the diabetic tolerates milk sugar or fruit sugar better than glucose, this is soon found to be illusory.

The power of burning sugar—specifically d-glucose—is always impaired and usually markedly deficient in diabetes, though rarely entirely lacking. It is most likely, at present, that the most reasonable scheme for the normal combustion of d-glucose in the body

runs as follows: d-glucose > a glyoxal body > lactic acid > ethyl alcohol. From the point of ethyl alcohol, the combustion would occur as normally in the case of the administration of minute amounts of ethyl alcohol. Now, it has been shown positively that the diabetic is able to burn lactic acid and ethyl alcohol as well as the normal man; the combustibility of glyoxal has not been tested in the diabetic. From this fact it seems clear that the defect in the diabetic must lie either in the conversion of d-glucose into the somewhat hypothetical glyoxal body or in the conversion of the latter into lactic acid. Putting the matter briefly—disregarding the question of the intermediary stages between the sugar and lactic acid—we may say that the inability of the diabetic to burn sugar rests, chemically, upon his inability to convert d-glucose into lactic acid.

The cause of this defect is not clear. I believe that the well-known experiment of Cohnheim indicates that for the fermentation of glucose in the body the muscular system forms a ferment, analogous to the zymaze of the yeast. The action of this ferment when exposed directly upon sugar is slow. When, however, a properly prepared pancreatic extract is added to the system, the reaction is rapid. We would term the muscular substance the enzyme and the pancreatic secretion the zymo-excitor. A strict analogy is to be had in the example of the yeast. The zymaze acts quite slowly upon sugar, but in the presence of PO_4 ions it acts very rapidly. Here the zymaze is the ferment and PO_4 ions the zymo-excitor. What the substance in the pancreatic extract actually is that acts as the zymo-excitor for the muscle ferment for the combustion of sugar is not known. It is very difficult to secure the material in quantity, and although I have made some tentative experiments and analyses, the results have been negative. To those who wish to repeat the Cohnheim experiment, certain cautions may be permitted. In the first place, the muscular and pancreatic extracts must be made from absolutely fresh tissues, and the process must be done at a low temperature, just above the freezing point of water. It is true that negative results have been obtained. These negative results simply indicate that the experiment was a failure, but in no way reflect upon the positive results. Many investigators, MacFadyean for one, repeated

the Buchner experiment without success. There are yeasts from which a ferment cannot be successfully expressed, and there are apparently periods in the lifetime of all yeast cultures in which the ferment is present in very small amount. It is possible that the pancreas has periods of rest and periods of secretion. I have personally failed in the experiment, but I have also succeeded.

It is my personal belief that the present data warrant us in locating this internal secretion of the pancreas in the islands of Langerhans, and it is my conviction that typical diabetes is to be regarded as a disease due to the destruction or the non-functionation of these bodies, in accordance with the theory of Opie. The majority of pancreatic glands taken from cases of typical diabetes display a marked diminution or a complete absence of the islands of Langerhans. It is, of course, not necessary to assume that they must have been destroyed; many histologically normal cells of the secretory tubules and glomeruli are to be encountered in badly diseased kidneys, whose possessors have died of uremia. The occasional case in which the islands seem fairly numerous and of normal appearance proves nothing against the theory of Opie because of the frequent failures which are to be observed in any attempted parallelism between functionation and histological appearance, a situation strikingly enough demonstrable in the heart muscle.

The conversion of the sugar into glycogen is defective in nearly all cases of true diabetes. This holds true not only for the liver, but for the general muscular tissues as well. Ordinarily speaking, since there is little combustion of sugar in the body of the diabetic and the glycemia is above the normal, by the law of mass action we should except an increase in the formation of glycogen. That we observe a decrease is therefore all the more striking. The most reasonable, provisional, explanation of this would lie in the reduction of the glycogenase. That the diabetic is done an additional injury through this defect is obvious.

The formation of fat from sugar is also usually defective in the diabetic. From the standpoint of general physiology, fat may be termed the ultimate storage form of sugar. The method of the formation of fat from sugar is not known. It is a universal reaction of the animal and vegetable kingdoms. The reversed action, the

formation of sugar from fact, is of quite universal occurrence in plants. A few years ago Pflüger attempted to show that similar relations occur in the animal organisms, and Fischer has stated to me in conversation his conviction of the formation of sugar from fat in the animal organism. This, however, has not been proved experimentally or in any other way. We, on the other hand, are wholly in the dark as to the steps through which the body normally burns fat. The ordinary course of supposition that the higher fatty acids are burned by the cleavage of CH_2 groups, quite as the woodsman maintains his fire by chopping off piece after piece from the end of a long log, cannot be accepted in the direct sense. If it were true that fat is burned in the body only after being returned to the state of sugar, a number of the most pressing problems in diabetes would be nearer solution. The defect in the burning of fats, commonly observed in severe diabetes, would thus be simply the further expression of the inability of the same body to burn sugar. This inability of the diabetic to burn fat is revealed in the elimination of β-oxybutyric acid, diacetic acid, and acetone. Upon the assumption of the theory that normally fats are burned through sugar, we would assume that the transition to the sugar molecule would be through a fatty acid. In the case of the diabetic, this transition to the sugar from the fatty acid would be assumed to be defective, and instead, the lower fatty acid would be converted into β-oxybutyric acid, from which the other two naturally follow. An example may be seen in cystinuria, in which the cystin, which is normally oxidized to taurin, is converted into the diamine, cystin. Attractive as this general hypothesis is, it is entirely unproved. One thing must be insisted upon: the defect in the combustion of fats can no longer be assumed to be due, in a direct sense, to the defect in the combustion of sugar. First, because many instances are known in which these two combustions are entirely independent; and secondly, because they do not run parallel in the diabetic. While the hypothesis, which has today admittedly a wide following, that "fat can only be burned in a furnace of sugar," seemingly holds in many cases of diabetes, it is clear, as Lusk has shown, that in some cases of diabetes it can be experimentally proved not to hold.

CHANGES IN THE PROTEOLYTIC ENZYMES AND ANTI-ENZYMES OF THE BLOOD SERUM PRODUCED BY SUBSTANCES (CHLOROFORM AND PHOSPHORUS) WHICH CAUSE DEGENERATIVE CHANGES IN THE LIVER.

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The observations of Salkowski,[1] which have shown that incubated liver undergoes "self-digestion," have been extended to almost all tissues of the animal body. It is well known that the autolysis of most tissues occurs with maximum activity in a weakly acid medium. Biondi[2] has found that disintegration of liver is hastened by addition of weak acid, and Hedin and Rowland,[3] using the expressed juice of various organs, have noted that the spleen, kidney, and lymphatic nodes autolyze more actively in acid than in neutral or alkaline media. The trivial autolysis of voluntary muscle is not materially affected by acid or alkali, but the autolysis of heart muscle resembles that of other organs. Levine and Stookey[4] have found that autolysis of brain tissue and of testicle is favored by the presence of acid.

The pancreas is not an exception to the foregoing rule. The well-known observations of Heidenhain[5] have shown that trypsin, which exhibits maximum activity in alkali, exists in the pancreas as inactive zymogen, so that fresh extracts of the organ cause little proteolysis under conditions which favor the activity of trypsin.

[1] Zeit. f. klin. Med., 1890, xvii, suppl. 77.
[2] Virch. Arch., 1896, cxliv.
[3] Zeit. f. physiol. Chem., 1901, xxxii, 531.
[4] Jour. Med. Res., 1903, x.
[5] Pflüger's Arch., 1875, x, 557.

The conditions under which acid activates pancreatic extracts and their relation to the activation of pancreatic juice by enterokinase have been studied by one of us (Dochez).[1] Fresh pancreatic tissue which undergoes active autolysis in the presence of weak acid suffers little change in neutral solutions, and is almost unchanged after incubation in an alkaline medium, of which the concentration agrees with that most favorable to the action of trypsin (0.2 to 0.4 per cent. sodium carbonate). Heidenhain has shown that acid converts tryptic zymogen of fresh pancreas into trypsin; pancreas subjected to the action of acid acquires the power to digest under conditions which are favorable to trypsin, namely, in neutral or alkaline media. Although splenic substance autolyzes with greater activity in acid than in alkali, Hedin[2] has obtained in relatively putrified form two enzymes, one of which, designated α-lienoprotease, acts in alkali, whereas the other, designated β-lienoprotease, acts in acid. If fresh spleen (Hedin[3]) is temporarily subjected to the action of weak acid, its ability to autolyze in the presence of alkali is materially increased. Pre-treatment with acid makes active an enzyme which digests in the presence of alkali.

Dochez[4] has studied the modification of hepatic autolysis, which occurs as the result of changes in reaction, and has compared autolysis of liver with autolysis of fresh pancreas. Whereas fresh liver autolyzes with greater activity in acid (0.2 per cent. acetic acid) than in neutral or alkaline media (from 0.2 to 0.4 per cent. sodium carbonate), liver which has been treated with weak acid during twenty-four hours acquires the power to autolyze or to digest casein in alkaline medium with equal or greater activity than in acid. Other evidences cited by Dochez shows that the liver contains two enzymes, one of which acts in acid, whereas the other, favored by alkali, is active only after the tissue has been subjected to acid. Vernon[5] has shown that pancreatic extracts become active after standing. Dochez has likewise noted that liver tissue allowed to stand on ice gradually acquires the power to autolyze in the presence of alkali.

[1] Proc. of Soc. for Exper. Biol. and Med., 1910.
[2] Jour. of Physiol., 1904, xxx, 155.
[3] Festschr. f. Olof. Hammarsten, Upsala, 1906, vi.
[4] Jour. of Exper. Med., 1910, xii, 666.
[5] Jour. of Physiol., 1901, xxvi, 269.

It is noteworthy that the polynuclear leukocytes of an inflammatory exudate cause proteolysis with greater activity in alkali than in acid, and, unlike pancreas, liver, or spleen, and doubtless other organs, exhibit this activity in alkali when freshly obtained from the body; no pre-treatment with acid is necessary in order to bring this enzyme (leukoprotease) into action. The bone marrow, unlike other tissues, exhibits the same ability to digest with greater activity in alkali than in acid.

The power of the blood serum to restrain the activity of tryptic digestion has long been known. Hahn[1] made the observation that trypsin fails to digest fibrin or gelatin when fresh blood serum is present. He has found this power to inhibit lost if blood serum is heated to a temperature of 65° C. The inhibiting substance is apparently attached to the proteins of the serum, but is not a common property of all proteins of the blood, for the globulin fraction of the serum, precipitated by half saturation with ammonium sulphate, fails to restrain the action of trypsin, whereas the albumin fraction precipitated by complete saturation after globulin has been removed exerts a retarding influence.

Ascola and Bezzola,[2] in 1903, doubtless influenced by the observations of Fr. Müller[3] upon self-digestion of lung consolidated by pneumonia, have sought to determine if this inhibiting property of the serum undergoes any alteration during the progress of pneumonia. They have claimed that there is at first a marked increase of antitryptic action; this increase is maintained for a time, and after crisis is followed by decrease, often occurring in association with disappearance of the local lesion. The subject attracted little attention until Brieger and Trebing[4] showed that there is an almost constant increase of the antitryptic activity of the blood serum in association with carcinoma. Subsequent studies have demonstrated that this increased anti-enzymotic activity is apparently dependent upon the accompanying cachexia rather than upon the newgrowth itself, and a similar change has been observed in association with a variety of diseases, such as pneumonia, typhoid fever, tuberculosis, and exophthalmic goitre, of which the common char-

[1] Berliner klin. Woch., 1897, xxxiv, 499.
[2] Ibid., 1903, xl, 391.
[3] Verhandl. d. XX Cong. f. inner. Med., 1902, p. 192.
[4] Berl. klin. Woch., 1908, lxv, 1041.

acter, according to K. Meyer,[1] is increased disintegration of the protein constituents of the body, perhaps referable to increased activity of proteolytic enzymes.

Finding that the serum in certain diseases associated with leukocytosis exhibits increased anti-enzymotic activity when tested with enzyme of polynuclear leukocytes, several observers (Bittorf,[2] Weins[3]) have maintained that the enzyme set free by leukocytes neutralizes the antibody of the serum and thus indirectly causes an excessive regeneration. Nevertheless, numerous observations have shown, on the one hand, that anti-enzymotic activity of the blood serum is not constantly increased in association with leukocytosis (K. Meyer), whereas, on the other hand, many conditions, such as malignant growth, tuberculosis, and typhoid fever, frequently accompanied by increase of anti-enzyme, usually exhibit no leukocytosis.

By a series of comparative tests, Jochmann and Kantorowicz[4] have shown that serum which exhibits high anti-enzymotic activity toward trypsin shows increased ability to restrain the activity of the enzyme of the polynuclear leukocytes, which, like trypsin, digests in the presence of an alkaline medium. Injection of trypsin into rabbits increases the ability of the serum to inhibit both trypsin and leukoprotease, and, furthermore, injection of leukoprotease has the same result.

The occurrence of increased anti-enzyme in the serum suggests the possibility that anti-enzyme is increased in order to balance an increased quantity of free enzyme. With this possibility in view, we have attempted to determine if the proteolytic activity of the blood serum undergoes any alteration during the course of chloroform poisoning so severe that advanced degenerative changes are produced in the liver. The possibility that such a study might prove fruitful has been suggested by the observation that the increase of antileukoprotease accompanies prolonged intoxication with chloroform or phosphorus.

The existence of proteolytic enzyme in normal blood serum has long been known. Delezenne and Pozerski[5] have found that blood

[1] Berl. klin. Woch., 1909, xlvi, 1064, 1890.
[2] Deut. Arch. f. klin. Med., vol. xcl.
[3] Ibid., 1901, xcl, 456.
[4] Zeit. f. klin. Med., 1908, lxvi, 153.
[5] Compt. rend. de la Soc. de Biol., 1903, lv, 327, 690, 693.

serum mixed with chloroform acquires the power to digest gelatin and casein. Hedin has shown that the globulin fraction of the blood serum of the ox, obtained by half saturation with ammonium sulphate, contains a weak proteolytic enzyme. The albumin fraction of the serum, obtained by complete saturation after removal of globulin, contains anti-enzyme, which in normal serum restrains the activity of the enzyme just mentioned. One of us[1] has shown (1905) that the anti-enzymotic activity of the blood serum is lost in the presence of 0.2 per cent. acetic acid; in this medium the blood serum exhibits well-marked proteolytic activity, but in neutral or alkaline media antibody balances enzyme and neither autolysis nor other proteolytic activity is demonstrable.

In order to determine what factors cause changes in the enzymotic and anti-enzymotic activity of the blood serum, a condition which can be produced experimentally offers obvious advantages, for the phenomena which occur can be repeatedly traced from the beginning through various stages of the process. Chloroform poisoning has proved especially favorable to this study, because it reproduces the increase of anti-enzyme heretofore frequently noted with the cachexia of carcinoma, with various infections, and with other diseases.

The changes in the liver which accompany prolonged administration of chloroform by inhalation are clearly defined by the recent studies of Howland and Richards,[2] which have directed our attention to this subject. There is necrosis implicating the central part of each hepatic lobule. Disintegration of protein within the body is shown by increased elimination of nitrogen and sulphur by the urine. When intoxication is not severe, there is, instead of necrosis, fatty degeneration of the liver, kidneys, heart muscle, etc. Doyon and Billet[3] have found that the blood may become incoagulable, and that incoagulability is associated with diminution of the fibrinogen contents of the serum.

We have followed the coagulability of the blood during the course of chloroform poisoning, produced by the daily administration by stomach of a given quantity of chloroform (1 or 2 c.c. per kilogram

[1] Jour. of Exper. Med., 1905, vii, 316.
[2] Ibid., xi, 344.
[3] Arch. de med. exper.

of body weight), and have found that the coagulation time of the blood increases during the first three days; in some instances the blood becomes wholly incoagulable. Hemorrhage into the gastro-intestinal tract or into the peritoneal cavity is not infrequent, and death often occurs at the end of three or four days. When poisoning is not acutely fatal, a reaction occurs; the coagulability of the blood rapidly regains its former activity, and even though the same daily dose of chloroform is administered, coagulation at the end of about a week after beginning of the experiment may have become somewhat more rapid than normal. An animal which has survived the critical period of three or four days may live ten or twelve days. The animal has established some form of resistance to the poison. In such instances there is widespread fatty degeneration of the liver and other organs and comparatively little necrosis.

The phenomena which have been described have a close analogy in phosphorus poisoning. There is, it is well known, intense fatty degeneration of the liver, with some necrosis, and in some instances, as Jacoby[1] has shown, diminution of the coagulability of the blood is associated with the disappearance of fibrinogen. Furthermore, Jacoby has found that the liver with phosphorus poisoning undergoes more rapid autolysis than normal liver. He suggests that enzyme, set free by the liver, dissolves the fibrinogen of the blood. Our observations, mentioned above, suggest that changes which occur in the blood as the effect of chloroform or phosphorus may be subject to considerable variation, dependent upon the severity of intoxication and upon the length of the period of administration.

Gradual increase of anti-enzyme for a proteolytic enzyme, namely, leukoprotease, during the progress of intoxication with chloroform and phosphorus, noted at the beginning of our experiment, has suggested the possibility that disintegrating liver tissue may set free those proteolytic enzymes which are demonstrable in normal liver. The attempt has been made to determine if at any stage of intoxication the serum exhibits increased proteolytic activity. The enzymotic content of the serum has been tested by incubating a fixed quantity of blood serum during four or five days at 37° C. and subsequently determining the degree of autolysis, or by incubating

[1] Zeit. f. physiol. Chem., 1900, xxx, 174.

a fixed quantity of serum with a suitable protein substrat such as heated blood serum. The hepatic enzyme, which is most readily demonstrated, digests in the presence of acid. To determine if the similar enzyme which exists in the blood undergoes any change during the progress of chloroform intoxication, a series of experiments has been performed on dogs.

A fixed quantity of blood has been subjected to autolysis in the presence of 0.2 per cent. acetic acid. Blood has been drawn at intervals of three or four days by means of a needle inserted through the skin into the jugular vein. A measured amount of serum, obtained by centrifugalization of the whipped blood, has been diluted with salt solution (0.85 per cent.) and acetic acid in such proportion that the final volume of 25 c.c. contains 0.2 per cent. acetic acid. In some instances blood serum denaturalized by heat has been added to the mixture as substrat for the proteolytic enzyme of the serum. All mixtures have been incubated during four or five days at 37° C. A mixture containing the same ingredients has served as control and has been immediately heated to boiling. After coagulation by heat, the coagulum has been removed by filtration and nitrogen in the filtrate has been determined by the Kjeldahl method; the amount of nitrogen liberated by digestion of coagulable protein will be expressed in cubic centimeters of one-tenth normal sulphuric acid.

In some experiments autolytic activity of serum from an animal receiving daily doses of chloroform has been tested on different days; the first test made before administration of chloroform serves as a normal standard for comparison, with subsequent changes. In other instances the serum of animals which have received chloroform has been compared with normal serum from another animal. Repeated tests have demonstrated that autolysis in neutral or alkaline media, under conditions otherwise similar to those just described, fails to occur or is much less marked than autolysis in the presence of acid.

Experiment. A dog (weight 6950 grams) received on two successive days 10 c.c. of chloroform. Coagulation time of the blood before administration of chloroform was four minutes five seconds. On the third day of the experiment the animal was sick and the blood failed to coagulate within one hour. The

following figures represent autolysis in the presence of acid before and after administration of chloroform; to obtain further information concerning the changes which have occurred, serum obtained on the third day has been compared with the serum of a normal dog.

	Autolysis of 5 c.c. of serum during 4 days at 37° C.			
	Control.	In neutral medium.	0.2% sodium carbonate.	0.2% acetic acid.
Serum of chloroform dog before administration of chloroform—first day, normal serum	1.25			3.0
Serum of chloroform dog on third day	1.5	1.7	2.5	6.45
Serum of normal dog . .	1.75	1.75	2.05	3.6

The administration of chloroform has caused well-marked increase in the autolytic activity of blood serum tested in acid, and little change when tested in alkaline (perhaps trivial increase) or in neutral medium.

Since the quantities subjected to autolysis are small, experiments have been multiplied, with the purpose of establishing the accuracy of the result. These experiments confirm the experiment which has been described. They demonstrate that the well marked increase of proteolytic activity exhibited by animals which have received chloroform attains its maximum on the third or fourth day of intoxication, and tends to be greatest when intoxication is most severe and delay of coagulation time considerable. Increased activity of autolysis may be absent when the critical period of intoxication has passed or when the injurious action of chloroform has been slight.

It is noteworthy that the coagulation time of the blood is a fair index of the intoxication caused by chloroform. There has been a fairly close relationship between coagulation time and autolytic activity both in an acid and in an approximately neutral medium.

Having in view the possibility that degenerative changes in the liver are associated with increased activity of proteolytic enzymes, we have undertaken a series of experiments to determine if the blood serum of animals receiving chloroform or phosphorus exhibits any alteration of the normal power of blood serum of the dog to restrain

the autolysis of liver. Blood serum has inhibited autolysis in slight degree but no noteworthy change of inhibition has been caused by administration of chloroform.

In other experiments fresh liver of the rabbit has been subjected to autolysis in the presence of serum of normal rabbit and of serum of a rabbit poisoned with phosphorus, but there has been no constant or noteworthy difference. In a subsequent experiment the liver of an animal which has received phosphorus has been allowed to undergo autolysis. The attempt has been made to determine if serum of an animal similarly treated with phosphorus differs from normal serum in its effect upon the autolysis of the phosphorus liver. Both normal and phosphorus serum have inhibited autolysis of this liver, but the experiment offers little evidence that the antienzymotic activity of the phosphorus animal has undergone any significant change.

Far more constant results have been obtained when the serum of animals which have received chloroform has been allowed to act upon an enzyme which, unlike the autolytic enzyme of the liver, acts with greatest activity in an alkaline medium. Various quantities of serum from animals which have received chloroform and of serum from normal animals have been allowed to act upon a fixed quantity of enzyme of polynuclear leukocytes (leukoprotease). Leukoprotease (20 mg.) has been allowed to digest coagulated blood serum both alone and in the presence of normal and of chloroform serum.

Small quantities (0.2 and 0.5 c.c.) of normal serum produce almost no effect upon the enzyme, yet the same quantities of chloroform serum greatly diminish its activity. Continued increase of antienzymotic activity of the blood serum is well seen in the following experiment, in which tests, repeated at intervals of three days, have been made with the serum of an animal to which chloroform has been administered daily.

Experiment.—A dog (weighing 4750 grams) has received daily during eleven days (the sixth day excepted) 12 c.c. of chloroform. From 25 to 35 c.c. of blood have been drawn at intervals of three days. Coagulation time: First day, five minutes eighteen seconds; fourth, four minutes forty-three seconds; seventh, two minutes seven seconds; tenth, three minutes fifteen seconds. On the

fifth day there has been slight jaundice, which has subsequently increased in intensity. The inhibition of 20 mg. leukoprotease, caused by 0.5 c.c. of serum, is shown by the following figures:

	After incubation during 5 days at 37° C.
20 mg. leukoprotease and coagulated blood serum	17.25
Same mixture and 0.5 c.c. serum on first day (normal) . .	13.75
" " " fourth day	12.45
" " " seventh day	5.25
" " " tenth day	2.9

The administration of phosphorus has the same effect upon the anti-enzymotic activity of the blood serum as administration of chloroform. Increased inhibition of leukoprotease demonstrable in the serum of dogs which have received chloroform or phosphorus has been found in rabbits as well.

Under the influence of a poison such as chloroform, acting with intensity sufficient to cause necrosis of the liver and diminish the coagulability of the blood, the blood serum acquires increased ability to cause digestion of protein. This increased proteolysis is, in part at least, referable to an enzyme which, like the autolytic enzyme of the liver and almost all other organs, digests with maximum activity in a weakly acid medium. It is not improbable that proteolytic enzyme is liberated by disintegration of parenchymatous cells and carried away by the blood.

In animals which survive the severe intoxication produced by large doses of chloroform, or in those which have repeatedly received smaller doses, the blood serum acquires increased ability to restrain the action of a proteolytic enzyme; but this anti-enzymotic action is exerted not upon the enzyme of the liver, which acts in acid, but upon an enzyme which acts in the presence of alkali, namely, leukoprotease. There is little reason to doubt that the same serum will restrain the action of a second enzyme which acts in alkali, namely, trypsin; for, on the one hand, Jochmann and Kantorowicz have found that anti-enzyme for enzyme of leukocytes and for trypsin increases simultaneously; and, on the other hand, K. Meyer has found the antitryptic activity of the serum increased in animals

which have received phosphorus. Anti-enzyme for one type of enzyme is increased; whereas, evidence heretofore available indicates that a second type of enzyme is predominant in those tissues which are subject to the destructive action of the poison. Furthermore, our experiments have shown that an enzyme similar to that of the injured organ accumulates in the blood serum. It is difficult to correlate these observations.

Nevertheless, the experiments of Hedin and of Dochez show that the liver contains a second enzyme which, unlike that directly obtainable from fresh liver, digests protein in the presence of an alkaline medium. These observations suggest the possibility that this enzyme may have a part in changes which increase the anti-enzymotic activity of the blood serum after administration of substances injurious to the liver. Treatment of fresh liver with acid discloses an enzyme which digests in the presence of acid. Does the serum of an animal which has received repeated doses of chloroform and exhibits increased power to inhibit leukoprotease, and doubtless trypsin, exhibit as well increased power to inhibit that enzyme of the liver which is similar to these two enzymes? The experiments which will be described have been undertaken with the purpose of answering this question.

Using the method, described by one of us (Dochez), that enzyme which digests protein in the presence of alkali has been obtained by subjecting fresh liver to the action of weak acetic acid during a period of twenty-four hours. Liver just after removal, with aseptic precautions, from an etherized animal, has been finely ground by means of a hashing machine; ground liver has been mixed with twice its volume of salt solution, to which acetic acid has been added in such amount that the concentration of the mixture is 0.2 per cent. After this mixture has stood at a temperature slightly above freezing during twenty-four hours, the acid has been neutralized by an equivalent quantity of tenth normal sodium hydroxide. Ten cubic centimeters of this neutralized mixture has been allowed to undergo autolysis, and the inhibition caused by various quantities of serum has been tested. In order to determine if the inhibitory activity of serum is increased during the progress of chloroform poisoning, normal serum has been compared with serum obtained after repeated

administration of chloroform. For the purpose of the present investigation a comparative study of anti-enzymotic activity for leukoprotease and for enzyme of liver has been essential, and parallel tests of the action of each serum upon the two enzymes have been made.

In the following experiment, serum of an animal which has received chloroform is compared with that of a normal dog.

Experiment.—A dog, weighing 21 kilos, has received daily doses of chloroform, increasing from 0.5 to 7 c.c. Blood has been drawn on the fourteenth day of the experiment. Inhibition of leukoprotease and of enzyme of liver are compared.

Leukoprotease (20 mg.) acting on substrat causes proteolysis, represented by 16.6 c.c. $\frac{N}{10}H_2SO_4$, control being 1.5. Autolysis of the liver employed is represented by 27.2 c.c. $\frac{N}{10}H_2SO_4$, control being 16.05 c.c. In order to make the degree of inhibition more conspicuous, the control has been subtracted from the figure obtained after digestion during four days at 37° C.

	Total digestion with leukoprotease + 0.5 c.c. serum.	Total autolysis of liver: + 0.5 c.c. serum.	+ 1 c.c. serum.
With serum of normal dog	14.9	12.7	12.15
With serum of chloroform dog . . .	2.8	8.45	9.75

Well-marked increase of anti-enzyme for liver pre-treated with acid corresponds with increased anti-enzyme for leukoprotease. In the following experiment, identical in other respects with that just described, the effect upon autolysis of pre-treated liver, both of normal serum and of serum from a dog which has received chloroform, has been tested in the presence of alkali.

Experiment.—The foregoing experiment has been repeated by comparing serum of a normal dog with the serum of a dog (weighing 21 kilos), which has received 21 c.c. of chloroform daily (the seventh day excepted) during ten days.

Leukoprotease and suspension of liver have been employed, and the control has been subtracted from the figure obtained after digestion during four days at 37° C.

	Total digestion with leukoprotease + 0.5 c.c. serum.	Total autolysis of liver: + 0.5 c.c. serum.	+ 1 c.c. serum.
With serum of normal dog	13.2	15.65	13.8
With serum of chloroform dog . . .	4.67	12.9	12.85

These and other experiments show that the power of the serum to inhibit the active enzyme of acid-treated liver exhibits an increase parallel with the increased power to inhibit leukoprotease

The experiments which have been described show that chloroform, given in quantity sufficient to produce profound intoxication, indicated by necrosis of the liver and loss of coagulability of the blood, causes an increase of the proteolytic enzyme normally present in the blood serum. Increase of proteolytic activity is exhibited in the presence of weak acid, but is much less evident in an alkaline or neutral medium. This observation suggests the possibility that the proteolytic enzyme of liver tissue, which causes autolysis, and has maximum activity in the presence of acid, is freed by disintegration of hepatic cells and accumulates in the blood serum.

The anti-enzymotic action of the blood serum has been tested in animals which have repeatedly received chloroform in quantity insufficient to produce fatal intoxication. There is no increase of the normal power of the serum to restrain autolysis of liver. Nevertheless, when anti-enzymotic action of blood serum is tested with leukoprotease, gradually increasing activity constantly accompanies continued administration not only of chloroform but of phosphorus as well. On the one hand, it is especially noteworthy that the enzyme of leukocytes digests protein in an alkaline or neutral medium; whereas, the proteolytic enzyme of liver exhibits maximum activity in acid. On the other hand, it is now known that treatment of liver with weak acid renders active an enzyme which digests with energy an alkali in much the same way that treatment of fresh extract of pancreas with acid transforms pancreatic zymogen into trypsin. Is increase of anti-enzyme for leukoprotease an index of increase of anti-enzyme for this second enzyme of liver which, like leukoprotease, digests protein with maximum activity in alkali, and is, perhaps freed by disintegration of liver cells? Tests with acid-treated liver show that anti-enzymes for the hepatic enzyme which digests in alkali is increased during the progress of chloroform intoxication, and parallel tests with leukoprotease and with this hepatic enzyme have shown that serum which exhibits increased inhibition of one exhibits increased power to restrain the other.

The following scheme represents the relationship of hepatic enzymes to enzymes and anti-enzymes of the serum which is suggested by the foregoing experiments:

Proteolytic enzymes of liver.	Proteolytic enzymes of blood serum.	Anti-enzymic action of blood serum.
(A) Enzyme digesting in acid.	(A) Enzyme digesting in acid. *Increased by chloroform.*	(A) Alkalinity of serum.
(B) Enzyme digesting in alkali. (Made active by acid-treatment of fresh liver.)	(B) Enzyme digesting in alkali. (Present in globulin fraction of serum and inhibited by anti-enzyme of albumin fraction.) *Perhaps increased by chloroform but neutralized by increased anti-enzyme.*	(B) Anti-enzyme for trypsin leukoprotease and the similar enzyme of liver. *Increased by chloroform.*

Increase of anti-enzyme occurring in association with intoxication by chloroform or by phosphorus is doubtless similar to that which has been repeatedly observed with the cachexia of malignant growth, with various infections, and with other conditions. The increased protein disintegration which accompanies such processes is, perhaps, associated with liberation of proteolytic enzymes similar to those concerned in the postmortem autolysis of organs. The experiments which have been described suggest that formation of anti-enzyme is a means by which the body is protected from enzymes liberated by degeneration of cells.

A STUDY OF THE INTERNAL FUNCTION OF THE PANCREAS IN CARBOHYDRATE METABOLISM.[1]

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A recent study[2] showed that rapid atrophy and sclerosis of the entire pancreas is produced by occluding all the ducts and separating the pancreas from the duodenum. In a dog killed two months after the operation the gland was reduced to a small mass of dense fibrous tissue. On microscopic examination small areas of pancreatic acini were seen surrounded by connective tissue. Dr. Ordway, who made a careful histological study, failed to find any remains of the islands of Langerhans in the atrophied gland.

According to the theory most generally accepted, the islands of Langerhans furnish an internal secretion to the blood that enables the organism to destroy sugar. The association of lesions of the islands and diabetes was observed by Opie[3] and Ssobolew[4] in 1900. Since that time many investigators have studied the nature and frequency of the pathological changes of these structures in diabetes, and definite lesions of the islands have been found in a large proportion of the cases. It is held that if the islands cease to furnish the internal secretion, the sugar in the blood will not be consumed and diabetes will result.

In the observation cited above the dog did not develop diabetes in spite of the fact that the atrophy of the pancreas was extreme and the islands were destroyed. As our finding could not be explained by the island theory of diabetes, it was deemed important to inquire

[1] Investigation made with the aid of a grant from the Proctor Fund for the Study of Chronic Diseases.

[2] Pratt, Lamson, and Marks, Trans. Assoc. Amer. Phys., 1910, xxiv, 266.

[3] Jour. Bost. Soc. Med. Sciences, 1900, iv, 251; Jour. Exp. Med., 1901, v, 397.

[4] Zentralbl. f. allg. Path. u. path. Anat., 1900, xi, p. 202.

further into the effect of atrophy of the pancreas on carbohydrate metabolism. The limit of assimilation was determined in normal dogs and in animals in which atrophy of the pancreas had been produced.

I. Limit of Assimilation for Glucose in Normal Dogs. F. Hoppe[1] fed dogs with large amounts of cane sugar up to 200 grams, but never detected a trace of sugar in the urine. Claude Bernard,[2] on the other hand, observed glycosuria after feeding dogs with smaller amounts of cane sugar (40 to 80 grams per dog).

The first exact determinations of the limit of assimilation for carbohydrates in normal dogs were made by F. Hofmeister.[3] His figures are surprisingly low.

Table I.—*Hofmeister's Experiments.*

Weight.	Amount of glucose which produced glycosuria.	Limit of assimilation.	Per kilo.
Dog A, 2750 grams.	7.0 grams.	6 grams.	2.2 grams.
Dog B, 3400 grams.	10.0 grams.	8 grams.	2.4 grams.
Dog C, 1900 grams.	10.0 grams.	8 grams.	4.2 grams.
Dog F, 5400 grams.	16.2 grams.	...	Less than 3.0 grams.
Dog G, 3850 grams.	5.0 grams.	...	Less than 1.3 grams.

W. Schlesinger[4] found the limit of tolerance for glucose to be 10 to 11 grams per kilogram of body weight. Boeri and De Andries[5] gave the limit as 4 to 6 grams per kilo when the glucose was given to a fasting animal. There was a rise to 10 to 13 grams when the sugar was fed with other food.

Quarta[6] claims that the limit is much lower for male than female dogs. Tests made on four male dogs showed the average limit of tolerance to be 4.06 grams per kilo, while the average obtained in experiments on three female dogs was 10.28 grams per kilo.

De Filippi[7] gave two dogs, of equal weight, 12,250 grams, after they had been fasting eighteen hours, 100 grams of pure glucose, dissolved in 500 grams of water without other food. Neither dog developed glycosuria. When the dose was increased to 125 grams the urine of one of the dogs remained free from sugar, while the

[1] Virchow's Archiv, 1856, x, 144.
[2] Leçons sur le diabête, Paris, 1877, pp. 270, 320.
[3] Archiv f. exp. Path. u. Pharmacol., 1889, xxv, 240; xxvi, 355.
[4] Wien. klin. Wochenschr., 1902, p. 30.
[5] Policlin. V, Med., 1898, p. 477. Cited by De Filippi.
[6] Unpublished work, quoted by De Filippi.
[7] Zeits. f. Biologie, 1907, xlix, 511.

other showed within two hours a slight glycosuria. The limit of tolerance was more than 8.2 grams per kilo for one dog, and more than 12 grams for the other. De Filippi states that in an earlier investigation he gave to each of four normal dogs 100 grams of glucose in the morning on a fasting stomach. None of the animals developed glycosuria.

In Table II are given the results obtained by Pflüger.[1]

TABLE II.—*Pflüger's Experiments.*

Weight.	Amount of glucose which produced glycosuria.	Limit of assimilation.	Per kilo.
Dog I, 11,900 grams	.....	More than 200 grams	More than 16.8 grams
Dog II, 9,000 grams	.....	More than 100 grams	More than 11.1 grams
Dog III, 11,700 grams	225 grams	200 grams	17.1 grams
Dog IV, 7,900 grams	.....	More than 100 grams	More than 12.6 grams
Dog V, 13,000 grams	.....	More than 150 grams	More than 11.5 grams

The first three dogs (I, II, III) in this series were animals from which the duodenum had been removed; the remaining two (IV, V) were normal. Pflüger was struck with the great variation between his results and those of Hofmeister. The latter investigator added the glucose to a thin meat soup, and when fed in this form it was more rapidly absorbed than when given with chopped meat as was the mode of administration adopted by Pflüger. In tests made on one animal, Pflüger found that the limit of assimilation was lowered from "more than 11.5 grams" to "less than 8 grams" per kilo of dog weight when the sugar was given in soup instead of with hashed meat.

It will be seen that Hofmeister's figures are much lower than those obtained by other investigators. No satisfactory explanation of this has been brought forward. It was certainly not due entirely to the fact that the sugar was given under conditions that favored rapid absorption, for De Filippi, who gave it in water without other food, obtained higher limits of assimilation, as did Pflüger in his single experiment with thin soup meat.

METHODS. We added the glucose to weighed amounts of finely chopped beef heart, and after adding about 100 c.c. of water the

[1] Arch. f. d. ges. Physiol., 1908, cxxiv, 1.

sugar and meat were thoroughly mixed. Commercial glucose was used. This was tested, and found to contain 95 per cent. pure glucose. Except during the early part of the investigation a standard diet was given, composed of 300 grams of meat and 300 c.c. of milk on the day preceding the experiment. The animals were kept in metabolism cages, and the temperature of the room noted. The amount of sugar in the urine was determined by the polariscope. The limit of assimilation was calculated for pure glucose.

The details of the tests on four normal dogs are given in Tables III, IV, V, and VI.

TABLE III.—*Dog VI.*

Date.	Weight of dog in grams.	Food.	Sugar.	Amount of urine in c.c.	Amount of sugar.	Notes.
March 18, 1909	5300	Meat plus 10 grams glucose	0	530		
March 19, 1909	..	250 grams meat 10 grams lard 25 grams glucose	—	560		
March 20, 1909	..	250 grams meat 10 grams lard 30 grams glucose	—	420		
March 21, 1909	..	250 grams meat 10 grams lard 35 grams glucose	—	440		
March 22, 1909	..	500 grams meat 10 grams lard 45 grams glucose	—	475	....	Fehling's solution turned green.
March 23, 1909	..	250 grams meat 10 grams lard 45 grams glucose	—			
March 24, 1909	..	Morning—small amount of meat 55 grams glucose Evening— 250 grams meat 100 grams milk 75 grams glucose	— +	... 425	.... 0.64	Urine voided during the day free from sugar. Polariscope 0.15%.

The limit of assimilation was more than 9.8 grams per kilo of body weight.

TABLE IV.—*Dog VII, female.*

Date.	Weight in grams.	Food.	Sugar.	Specific gravity.	Amount of urine in c.c.	Amount of sugar in grams.	Notes.
January 24, 1910	6400	200 grams meat 200 c.c. milk					
January 25, 1910	..	300 grams meat 75 grams glucose	—	1025	460	..	Temperature of room, 20° C.
January 31, 1910	..	200 grams meat 200 c.c. milk					
February 1, 1910	..	300 grams meat 90 grams glucose	+	1055	212	0.6	

The limit of assimilation was more than 11.1 grams per kilo of body weight.

TABLE V.—*Dog VIII, male.*

Date.	Weight in grams.	Food.	Sugar.	Specific gravity.	Amount of urine in c.c.	Amount of sugar.	Notes.
Feb. 25, 1910	13,300	300 grams meat 75 grams glucose	—	1019	535	..	Room temperature, 90.4° C.
Mar. 1, 1910	..	300 grams meat 100 grams glucose	—	1022	575		
Mar. 5, 1910	..	300 grams meat 125 grams glucose	+	1025	840	Trace	Room temperature, 20° C.
Mar. 9, 1910	..	300 grams meat 115 grams glucose	—	1029	375		
Mar. 11, 1910	..	300 grams meat 120 grams glucose	—	1025	905	..	Room temperature, 14.4° C.
Mar. 15, 1910	11,900						

The limit of assimilation was 9.5 grams per kilo.

TABLE VI.—*Dog IX, female.*

Date.	Weight of dog in grams.	Food.	Sugar.	Specific gravity.	Amount of urine in c.c.	Amount of sugar in grams.	Room temperature.
March 8, 1910	7600	300 grams meat 300 c.c. milk					
March 9, 1910	..	300 grams meat 85 grams glucose	—	1049	200	..	15° C.
March 14, 1910	..	300 grams meat 300 c.c. milk					
March 15, 1910	..	300 grams meat 95 grams glucose	—	1029	300	..	19.4° C.
March 16, 1910	..	300 grams meat 300 c.c. milk					
March 17, 1910	..	300 grams meat 110 grams glucose	—	1049	195	..	17.3° C.
March 31, 1910	..	300 grams meat 300 c.c. milk					
April 1, 1910	..	300 grams meat 125 grams glucose	+	1054	155	4.75	22.2° C.
April 3, 1910	..	300 grams meat 300 c.c. milk					
April 4, 1910	..	300 grams meat 125 grams glucose	—	1060	148	..	21.1° C.
April 5, 1910	..	300 grams meat 300 c.c. milk					
April 6, 1910	..	300 grams meat 125 grams glucose	—	1052	175	..	23.8° C.
April 11, 1910	..	300 grams meat 300 c.c. milk					
April 12, 1910	..	300 grams meat 135 grams glucose	+	1032	290	0.14	21.1° C.
April 13, 1910	..	300 grams meat 300 c.c. milk					
April 14, 1910	..	300 grams meat 135 grams glucose	—	1060	140		

The limit of assimilation was more than 15.6 grams per kilo of dog weight.

It will be seen by consulting Table VI that Dog IX developed glycosuria on April 1, when 125 grams of glucose were fed, but in two subsequent tests the urine remained free from sugar when this amount of glucose was given. This is probably explained by the fact that the dog was allowed to run about in a yard on the day

preceding the feeding of sugar, April 3 and April 5. In March the dog was kept in her cage most of the time. From April 6 to 10, considerable exercise was given. On April 11 she was confined in a cage and the following day was fed 135 grams of glucose. Slight glycosuria developed. On April 13 she was allowed the freedom of the "run," and the usual preliminary diet given. Although 135 grams of glucose were given on April 14, the urine remained free from sugar. These observations show that exercise prior to the day of the feeding experiment may alter the limit of assimilation.

Our results on normal dogs, which are summarized in the following table, accord with those reported by Boeri and De Andries, Schlesinger, and Pflüger.

TABLE VII.—*Limit of Assimilation for Glucose Per Kilo of Body Weight in Normal Dogs.*

Dog VI	More than 9.8 grams.
Dog VII	More than 11.1 grams.
Dog VIII	9.5 grams.
Dog IX	More than 15.6 grams.
Average	More than 11.5 grams.

II. LIMIT OF ASSIMILATION FOR GLUCOSE IN DOGS WITH ATROPHY OF THE PANCREAS. As stated in the beginning of this paper, Pratt, Lamson, and Marks[1] have shown that if all the pancreatic ducts are occluded extreme atrophy of the gland occurs. The absorption of fats and proteins is so seriously affected that the animals lose weight rapidly.

Dog V. Young female. Weight, 5700 grams.

On November 19, 1908, Dr. Murphy, under ether anesthesia, separated the pancreas from the duodenum, cutting all the tissues that unite the two except the main branches of the pancreatico-duodenal artery and vein, the preservation of which was necessary in order to prevent necrosis of the duodenum. Two pancreatic ducts were recognized, and these were cut between double ligatures. The omentum was inserted between the duodenum and the corpus pancreatis, thus interposing a barrier of living tissue through which pancreatic juice escaping from open ducts would have to pass before it could enter the intestine.

[1] Loc. cit., 277.

As soon as the dog began to eat meat the bulky stools contained a large amount of undigested muscle tissue. A metabolism experiment showed that only 31 per cent. of fat and 32.1 per cent. of nitrogen were absorbed. There was a steady loss of weight in spite of an abundant diet. On January 12 the weight had fallen to 4700 grams. The urine was repeatedly examined, but it was always free from sugar.

February 13. Weight, 5100 grams.

February 23. 10 grams of **glucose** added to the food, which consisted of meat and milk. The urine gave no reduction with Fehling's solution.

February 24. Urine contains no sugar.

February 26. 35 grams of **glucose** given with the regular food. Urine: amount, 650 c.c. Fehling's test positive.

February 28. Urine: 350 c.c.; specific gravity, 1027; slight trace of albumin; sugar present.

March 1. Urine is free from sugar.

March 2. Weight 5900 grams. Fed 30 grams of **glucose**. Two hours later voided 25 c.c. of urine containig 0.4 grams of sugar (quantitated with Fehling's solution). During the following twenty-four hours 610 c.c. of urine collected. This was free from sugar.

March 3. Urine, 975 c.c.; specific gravity, 1024; no sugar; slight trace of albumin.

March 4. No glucose given. Urine: 1700 c.c.; sugar present, 1.5 per cent. = 25.5 grams (Fehling's method).

March 5. Urine: 1000 c.c.; no sugar.

March 6. Urine: 575 c.c.; no sugar.

March 8. Weight, 6000 grams.

March 9 to March 29. Urine examined daily and found free from sugar.

April 24. Fed 30 grams of **glucose**, with 200 grams of meat and 225 c.c. of milk. Four hours later found 65 c.c. of urine, which contained 3.7 per cent of sugar, amount 2.4 grams. The urine passed later in the day was free from sugar.

April 28. Weight, 6400 grams.

May 12. Given 20 grams of **glucose** with 500 grams of meat and 250 c.c. of milk. In the evening 200 c.c. of urine had been collected which contained 0.6 gram of sugar.

May 29. Given 15 grams of **glucose**, with a meal consisting of 250 grams of meat and 250 c.c. of milk. During the day voided 440 c.c. of urine, which reduced Fehling's solution. Amount of sugar, 1.8 grams.

May 30. Urine: 460 c.c.; no sugar.

June 2. Weight, 6800 grams.

June 3. Food: 10 grams of **glucose**; 250 grams of meat. Urine free from sugar.

June 4. No glycosuria.

June 9. Food: 10 grams of **glucose**; 250 grams of meat. Urine passed later in the day contained no sugar.

June 11. Weight, 7000 grams.

July 1. Weight, 7000 grams.

July 6. Food: 15 grams of **glucose**; 250 grams of meat; 250 c.c. of milk. Urine: 265 c.c.; specific gravity, 1028. No reduction of Fehling's solution at the time test was performed, but after one hour fluid had a greenish color; the following day a yellow precipitate had formed and settled to the bottom of the tube.

July 14. Weight, 6900 grams.

July 28. Weight, 6300 grams.

September 24. Food: 300 grams of meat, 15 grams of **glucose**. Urine: 210 c.c.; specific gravity, 1039; no sugar.

September 27. Food: 1000 grams of meat, 30 grams of **glucose**. Urine: 700 c.c.; specific gravity, 1023; no sugar. Limit of assimilation more than 4.4 grams per kilo.

October 17. Weight, 6500 grams.

November 10. No food for twenty-four hours.

November 11. Food: 500 grams of meat, 35 grams of **glucose**. Urine, 260 c.c.; specific gravity, 1045; no albumin; trace of sugar.

November 12. Urine free from sugar.

December 1. Weight, 6300 grams.

December 6. Weight, 5100 grams.

December 13. Weight, 5800 grams.

January 5, 1910. Weight, 5300 grams.

January 11. Weight, 5100 grams.

January 12. Food: 300 grams of meat, 30 grams of **glucose**. Urine, 215 c.c.; 0.89 gram sugar. Limit of assimilation less than 5.6 grams per kilo.

January 24. Weight, 5000 grams.

January 25. Food: 300 grams of meat, 15 grams of **glucose**. Urine: 265 c.c.; no albumin; no sugar.

January 31. The dog is very thin and weak. She cannot go up more than one flight of stairs without resting, and is unable to jump from the floor into her cage, as she could formerly.

February 1. Weight, 4700 grams. Food: 300 grams of meat, 25 grams of **glucose**. Urine: 230 c.c.; specific gravity, 1038; no sugar. Limit of assimilation more than 5 grams per kilo.

February 3. Today the fresh pancreas of the sheep was added to the diet (the dog was given two or three glands a day.)

February 9. The dog is now very lively and apparently stronger than she has been for two months. The stools are small and firm, and do not contain any excess of fat. On microscopic examination only a few muscle fibres and no starch granules are seen. A metabolism experiment conducted over four days—February 8 to February 11—showed that 88.7 per cent. of the fat contained in the food was absorbed and 82.2 per cent. of the nitrogen.

February 14. Weight, 5300 grams.

February 18. Weight, 5800 grams. Food: 300 grams of meat, 300 c.c. of milk, two sheeps' pancreas.

February 19. Food: 40 grams of **glucose**, 300 grams of meat, two sheeps' pancreas. The dog appears ravenously hungry; she eats the pancreas first, picking the glands out from the mixture of pancreas and chopped beef heart. Urine: 275 c.c.; specific gravity, 1041; no sugar. Room temperature, 16.2° C.

February 21. Weight, 5900 grams.

February 23. Weight, 6000 grams. Food: preliminary diet with three pancreatic glands.

February 24. Food: 50 grams of **glucose**; 30 grams of meat, three pancreatic glands. Urine: 240 c.c.; specific gravity, 1049; no sugar.

February 28. Weight, 6400. The dog has never been in better condition.

March 3. Weight, 6400 grams.

March 8. Weight, 6600 grams. Preliminary diet of 300 grams of meat and 300 c.c. of milk, with three fresh pancreas.

March 9. 65 grams of **glucose**, with 300 grams of meat and three pancreas. Urine: 320 c.c.; specific gravity, 1040; no sugar. Room temperature, 15° C.

March 15. Weight, 6900 grams. The dog was fed today 80 grams of **glucose**, with 300 grams of meat and three pancreatic glands. Urine: 350 c.c.; specific gravity, 1039; no sugar. Room temperature, 19.5° C.

March 16. Food: 300 grams of meat, 300 c.c.; of milk, and three fresh pancreas.

March 17. Food: 100 grams of **glucose**, with 300 grams of meat and three pancreas. Urine: 240 c.c.; specific gravity, 1039. Sugar present, amount 0.81 gram. Temperature, 17.3° C.

March 18. Weight, 6900 grams. The feeding of the fresh pancreas was stopped today.

March 21. Food: 300 grams of meat and 300 c.c. of milk.

March 22. Weight, 6600 grams.

March 23. Food: 80 grams of **glucose**, with 300 grams of meat. Urine: 225 c.c.; specific gravity, 1040. No sugar. Room temperature, 18.9° C.

March 30. Weight, 6500 grams.

March 31. Preliminary diet of 300 grams of meat and 300 c.c. of milk.

April 1. Given 80 grams of **glucose**, with 300 grams of meat. Urine: 230 c.c.; specific gravity, 1031. No sugar. Temperature, 22.2° C.

April 3. Preliminary diet of 300 grams of meat and 300 c.c. of milk.

April 4. 100 grams of **glucose**, with 300 grams of meat. Urine: 230 c.c.; specific gravity, 1036; no sugar. Room temperature 21.1° C.

April 5. Regular preliminary diet.

April 6. Weight, 6000 grams. Fed 100 grams of **glucose** and with 300 grams of meat. Urine: 170 c.c.; specific gravity, 1054; no sugar. Room temperature 23.9° C.

April 11. Preliminary diet.

April 12. Weight, 5800 grams. Fed 100 grams of **glucose** with 300 grams of meat. Urine 285 c.c.; specific gravity, 1031; sugar, 1.45 grams. Temperature, 21.1° C.

April 21. Preliminary diet.

April 22. Weight, 5600 grams. Given 100 grams of **glucose,** with 300 grams of meat. Urine: 265 c.c.; specific gravity, 1034; no sugar.

April 26. Weight, 6200 grams.

April 29. Preliminary diet.

April 30. Given 100 grams of **glucose,** with 300 grams of meat. Urine: 300 c.c.; specific gravity, 1032; sugar, 2.01 grams.

May 1. Urine: 475 c.c.; specific gravity, 1020; no sugar. This dog has lived without any pancreatic secretion entering the intestine from November 19, 1908, until the present time. In one metabolism experiment 95.2 per cent. of the fat in the food was excreted in the feces.

TABLE VIII.—*Dog V. Pancreas Separated from Duodenum November* 19, 1908. *Young Female; Weight,* 5700 *Grams.*

Date.	Weight in grams.	Amount of sugar in food.	Limit of assimilation for glucose per kilo.[1]	Sugar in urine. Grams.	Notes.
March 2, 1909	5900	30 grams glucose 10 grams lactose — 40 grams	Less than 6.5 grams	+0.4	
May 12, 1909	6400	20 grams glucose 13 grams lactose — 33 grams	Less than 4.9 grams	+0.6	
May 29, 1909	6800	15 grams glucose 13 grams lactose — 28 grams	Less than 3.9 grams	+1.8	
June 3, 1909	6800	10 grams glucose	More than 1.6 grams	0	
June 9, 1909	7000	10 grams glucose	More than 1.2 grams	0	
July 6, 1909	7000	15 grams glucose 13 grams lactose — 28 grams	Less than 3.8 grams	+trace	
Sept. 27, 1909	....	30 grams glucose	More than 4.4 grams	0	
Nov. 11, 1909	6500	35 grams glucose	Less than 5.1 grams	+trace	
Jan. 12, 1910	5100	30 grams glucose	Less than 5.6 grams	+0.89	
Jan. 25, 1910	5000	45 grams glucose	More than 2.9 grams	0	Fresh pancreas fed from February 3 to March 18.
Feb. 1, 1910	4700	25 grams glucose	More than 5.0 grams	0	
Feb. 19, 1910	5800	40 grams glucose	More than 6.6 grams	0	
Feb. 24, 1910	6000	50 grams glucose	More than 7.9 grams	0	
March 9, 1910	6600	65 grams glucose	More than 9.3 grams	0	
March 15, 1910	6900	85 grams glucose	More than 11.7 grams	0	
March 17, 1910	6900	100 grams glucose	More than 13.8 grams	0	
April 4, 1910	6000	100 grams glucose	More than 15.8 grams	0	
April 12, 1910	5800	100 grams glucose	Less than 16.3 grams	+1.45	
April 22, 1910	5600	100 grams glucose	More than 16.9 grams	0	
April 30, 1910	6200	100 grams glucose	More than 15.3 grams	0	

[1] Calculated for pure glucose.

Atrophy of the pancreas takes place with rapidity after all the ducts are occluded, and Hess found sclerosis of the pancreas of high degree one month after the operation, and Pratt, Lamson, and Marks observed extensive atrophy and sclerosis in two months. As all the dogs have shown atrophy of the pancreas, varying in extent with the length of time after operation, there is every reason to believe that in Dog V there has been extreme atrophy of the pancreas for many months.

In spite of the progressive atrophy of the epithelial structures of the pancreas, the dog has not developed diabetes. A summary of the results in the glucose assimilation tests is given in Table VIII. The tolerance for carbohydrates was not determined previous to the operation on November 19, 1908. The first experiment, on March 2, 1909, about three and a half months after occlusion of the ducts, showed that the limit of assimilation was less than 6.5 grams per kilo, while the average assimilation in our normal dogs was more than 11.5 grams. This observation furnishes additional evidence of the important part played by the pancreas in carbohydrate metabolism. From the seventh to the ninth month after the onset of atrophy of the organ the assimilation was less than 3.9 grams per kilo. Then a slight increase occurred, and in the eleventh month (test made September 27) more than 4.4 grams per kilo were taken without producing glycosuria. The gain was slight, and near the end of the twelfth month the assimilation was less than 5.1 grams per kilo.

This study gives no support for the view that there is compensation by other organs when the internal function of the pancreas becomes inpaired.

No direct relation can be traced between the general condition and the power to assimilate sugar. In July, 1909, when the dog weighed its maximum and was strong and active, the limit of assimilation was less than 3.8 grams per kilo, while on February 1, 1910, when the weight had dropped to the minimum, the limit was more than 5 grams per kilo.

Dog. IV.—Male. Weight, December 2, 1908, 11,100 grams. The operation of occluding the ducts and separating the pancreas from the duodenum was performed by Dr. Murphy on December 12.

Metabolism experiments on this dog have been reported.[1] There was severe disturbance in the absorption of fats and proteins after the exclusion of the pancreatic juice from the intestine, and the dog lost weight rapidly. During January the urine occasionally caused a slight reduction of Fehling's solution.

February 22. Weight, 7800 grams.

February 23. Dog given 10 grams of **glucose**. The urine remains free from sugar.

February 24. Dog given 20 grams of **glucose**. No glycosuria.

February 26. Dog given 35 grams of **glucose**. The urine reduces Fehling's solution. Limit of assimilation less than 4.5 grams per kilo.

February 27. March 2. The urine each day reduced Fehling's solution, although no more glucose was fed.

March 3. Urine did not reduce Fehling's solution.

April 20. Weight, 7600 grams.

April 24. Food: 30 grams of **glucose**, 200 grams of meat, 225 c.c. of milk. No glycosuria resulted.

April 25. Food: 35 grams of **glucose**, 150 grams of meat, 10 grams of lard. Urine: 250 cc.; 0.6 per cent. sugar; amount, 1.5 grams.

May 11. Weight, 7800 grams.

May 16. Food: 30 grams of **glucose**, 250 grams of meat, 250 c.c. of milk. Urine free from sugar. Including in the estimation the lactose of the milk, the limit of assimilation is more than 5.1 grams per kilo.

June 3. Weight, 6600 grams. The dog was given 30 grams of **glucose**, with meat. In the afternoon 150 c.c. were found, which contained 4.5 grams of sugar. Limit of assimilation less that 4.3 grams per kilo.

June 4. Weight, 6400 grams. Urine: slightly acid; specific gravity, 1021; slight trace of albumin; no sugar. Sediment contained many red corpuscles; some leukocytes, and a few hyaline and finely granular casts.

On June 4 Dr. Murphy removed the dense inflammatory tissue which occupied the side of the pancreas. The outlines of the organ

[1] Pratt, Lamson, and Marks, loc. cit.

were completely lost. The sclerotic mass was identified as the remains of the pancreas by the dilated duct passing through it. In breaking up the dense adhesions the liver was torn.

June 5. The dog was found dead. He had passed 55 c.c. of urine. This was acid, and had a specific gravity of 1012. Fehling's solution was turned green, and after standing a slight deposit of yellow cupric oxide formed at the bottom of the test-tube. The polariscopic examination showed about 0.1 per cent. of glucose.

AUTOPSY, June 5, 1909, by Dr. Thomas Ordway.

Anatomical Diagnosis. Massive hemorrhage into the peritoneal cavity; sacculated periduodenal abscess, with fistula into duodenum; chronic fibrous peritonitis (adhesion of omentum, duodenum, pancreas, and liver); contusion of liver; distention of gall-bladder; acute and chronic pyelonephritis; atrophy of pancreas and dilatation of pancreatic duct.

Body is that of a fairly well-developed and poorly nourished, somewhat emaciated, young adult male dog. Weight, 6170 grams. There is marked rigor mortis; no edema. Between the ensiform and umbilicus in the median line is a recent incised wound sutured with interrupted sutures of silkworm gut. The edges are clean and agglutinated. Subcutaneous and thoracic abdominal fat very scant.

Peritoneal Cavity. Peritoneum is everywhere blood stained and the pelvis is filled with fluid blood. Pelvis and flanks contain about 60 c.c. of fluid blood. The omentum, duodenum, and liver are bound together by firm adhesions, forming a mass which is 6 by 5 cm. in size. On the outside this is blood-stained (apparently caused by attempt to break up adhesions at operation on June 4). No pancreatic tissue can be recognized. The lymph nodes in the vicinity of this mass are considerably enlarged. On section they are of a general dark red color. On the left hand and lower portion of the mass above referred to is a hemorrhagic stump, with apparently a dilated pancreatic duct in the centre. Incision into the mass discloses an irregular, sacculated abscess cavity surrounding the duodenum anteriorly, and laterally and communicating with the duodenum by the fistulous tract 2 cm. below the pylorus. For 10 cm. from this point the duodenum is markedly thickened, the wall varying from 0.3 to 1.2 cm. The mucosa is elevated, roughened,

reddened, and in places ulcerated. Serial sections through the thickened duodenal wall adjacent to the abscess and the mass of surrounding adhesions show no definite evidence of pancreatic tissue. Dilated ducts are found, about which is firm, fibrous tissue, in which is an occasional small punctum, possibly the remains of glandular tissue.

Pleural Cavities. Normal.

Pericardial Cavity. Normal

Heart. The right auricle and ventricle are much distended by cruor clot. All cavities are apparently moderately dilated, particularly on the right side. The myocardium, endocardium, and valves are normal.

Lungs. They are very pale, collapsed, and normally crepitant throughout.

Spleen. Weight and size normal (estimation). On the outer border are three or four slightly elevated, yellowish nodules varying from 1 to 4 cm. in diameter. On section these are sharply circumscribed, circular areas without definite softening.

Gastro-intestinal Tract. Stomach is empty; rugæ prominent; duodenum described above. The small intestine is collapsed and empty. The large intestine contains considerable slate-colored, pasty, fecal material.

Pancreas. See peritoneal cavity.

Liver. The right lobe is adherent at the lower portion to the mass above described. At one portion the adhesions are somewhat separated, leaving a hemorrhagic surface. Three cm. from the area of adhesions in the substance of the right lobe is a large nodule 3 by 2 cm. in diameter, considerably firmer than the liver tissue elsewhere. On section this is of a general grayish-yellow color, and had a somewhat fibrous appearance, being in marked contrast to the normal chocolate-brown liver parenchyma. The gall-bladder is enormously distended, measuring 5 by 6 by 3 cm. The common duct runs through the mass of adhesions about the duodenum, and is apparently pressed upon by the periduodenal abscess. Pressure upon the gall-bladder, however, causes thin, yellowish fluid to flow freely into the duodenum.

Kidneys. Weight, 90 grams. Capsule strips freely, leaving a smooth surface. On section the pyramids in their inner third have a distinctly vacuolated or finely fenestrated appearance. This increases as the pelvis is approached. The mucosa of the pelvis is roughened, reddish, and has a granular appearance. The pelves contain 0.5 c.c. of slightly turbid fluid.

Adrenals. Normal.

Bladder. Normal.

Genital Organs. Normal.

Aorta. Normal.

Organs of Neck. Thyroid gland: Both lobes are easily found and are equal in size, measuring 3.5 by 1.4 by 0.8 cm.

Microscopic Examination. Fragments of tissue removed by Dr. Murphy at operation show two small areas of pancreatic epithelium surrounded by dense connective tissue, in which, in places, are numerous polynucular leukocytes and dilated ducts. Sections of the proximal portion, including the duodenum and wall of abscess cavity, show marked acute and chronic inflammation and occasional groups of pancreatic cells.

A search of the literature fails to reveal an instance of such extreme sclerosis of the pancreas as developed in this case. On naked-eye examination no pancreatic tissue could be found. Microscopic examination showed only a few minute areas made up of acinar cells embedded in dense connective tissue. No islands of Langerhans were seen. Although there was almost total destruction of the pancreas, the dog assimilated three weeks before its death more than 5.4 grams of glucose per kilo. On the other hand, the profound effect of atrophy of the pancreas on carbohydrate metabolism was shown by the reduction of the limit of assimilation to less than 4.5 grams per kilo within three months after the onset of the atrophy. Slight variation in the tolerance occurred. There was no definite increase with the passage of time, and the last test made two days before the dog's death showed the limit of assimilation to be as low as it had been three months previously. The sigificance of the glycosuria following the removal of the pancreas is not clear, owing to the speedy death of the animal. Transitory glycosuria may follow severe operative procedures when the pancreas is healthy. So in

this case it may have been the result of the operation, although the conclusion that it was due to the removal of the few areas of pancreatic tissue that remained is more probable. No dog has ever failed to develop diabetes when the entire pancreas has been extirpated. The hypothesis that the organism will compensate in some way if the internal function of the pancreas is gradually lost has as yet no clear evidence to support it.

Dog VIII.—Male. Weight, March 15, 1910, 11,900 grams.

March 16. Operation under ether anesthesia by Dr. F. T. Murphy. The corpus pancreatis measured 11 by 2.7 cm., the processus uncinatus 8 by 2 cm., and the processus lienalis 8 by 3 cm. A duct was found near the centre of the corpus pancreatis. A wedge-shaped mass of gland tissue, 1 by 1 cm. in size, was left around this duct, with its base in contact with the duodenum. At the distal end of this mass the duct was cut between double ligatures. The remainder of the pancreas was entirely separated from the duodenum except for a few connecting bloodvessels which were left intact. Only two pancreatic ducts were recognized. The omentum was placed between the cut surface of the pancreas and the duodenum.

The dog made a rapid recovery.

March 20. Weight, 10,000 grams.

March 22. The abdominal wound is clean and dry. Food: 150 grams of meat, 400 c.c. of milk. The urine is high colored; specific gravity, 1019. There is a large amount of albumin. No sugar. The sediment contains many fresh red blood corpuscles and a large number of spermatozoa.

March 23. Urine smoky; albumin present; no sugar. The sediment contains a few fatty and brown granular casts, and many fresh and disintegrated red blood corpuscles.

March 30. The dog is active and strong, but looks emaciated. Weight, 8200 grams. Food: 100 grams of **glucose**, 300 grams of meat. Urine: 320 c.c.; specific gravity, 1036; no albumin; sugar, 0.63 per cent., amount 2.02 grams. The feces are normal in appearance, but contain an excess of muscle fibers; no fat visible.

March 31. Preliminary diet: 300 grams of meat and 300 c.c. of milk.

April 1. Food: 90 grams of **glucose** and 300 grams of meat

Urine: 295 c.c.; specific gravity, 1039; a slight trace of albumin; sugar, 0.61 per cent., amount 1.80 grams; sediment contains many red blood cells and a few spermatozoa; no casts found. Room temperature, 22.2° C.

April 3. Preliminary diet as before.

April 4. Food: 65 grams of **glucose**, 300 grams of meat. Urine, 265 c.c.; sugar, 0.14 per cent., amount 0.37 grams. Room temperature, 21.1° C.

April 5. Preliminary diet. The dog had the freedom of the yard.

April 6. Weight, 8400 grams. Food: 50 grams of **glucose**, 300 grams of meat. Urine, 225 c.c.; no sugar. Room temperature, 23.9° C.

April 11. Preliminary diet.

April 12. Food: 60 grams of **glucose** and 300 grams of meat. Urine: quantity not determined, as some was lost; sugar, 2.9 per cent. Room temperature, 21.1° C.

TABLE IX.—*Dog VIII. Summary of Glucose Feeding Experiments After Separating Pancreas from Duodenum.*

Date.	Weight in grams.	Amount of sugar in food.	Limit of assimilation for glucose per kilo.[1]	Sugar in urine.
March 30, 1910	8200	100 grams glucose	Less than 11.5 grams	2.02 grams.
April 1, 1910	..	90 grams glucose	Less than 10.5 grams	1.80 grams.
April 4, 1910	..	65 grams glucose	Less than 8.4 grams	0.37 grams.
April 6, 1910	8400	50 grams glucose	More than 5.6 grams	0
April 12, 1910	..	60 grams glucose	Less than 6.7 grains	Amount not determined.

Before the operation it was necessary to feed the dog 125 grams of **glucose** in order to produce glycosuria. Within three weeks after the onset of atrophy of the pancreas sugar appeared in the urine when 65 grams of glucose were given. This represented a decrease in the limit of assimilation from 10 grams per kilo to less than 7.9 grams.

Schulze,[2] Ssobolew,[3] and De Witt[4] claim that after occlusion of the

[1] Calculated for pure glucose.
[2] Archiv f. mikr. Anat. u. Entw., 1900, lvi, 491.
Virchow's Archiv, 1902, clxviii, 91.
[4] Jour. Exp. Med., 1906, viii, 193.

pancreatic ducts the islands of Langerhans remain intact. The statement that the acini degenerate, but the islands undergo no change has often been brought forward in support of the island theory of diabetes. If tying *all* the ducts leads to no pathological alterations in the islands, how can the rapid loss in the power of the pancreas to destroy sugar in the organism which was observed in this animal be explained? It would certainly be difficult for defenders of the island theory to reconcile the great reduction in the limit of assimilation with the observations of the investigators just cited. To shut off all the pancreatic secretion from the intestine is a difficult task, as has been pointed out by Hess.[1] It has been often attempted, but rarely accomplished. In dogs and cats in which we have prevented entirely the entrance of pancreatic juice into the intestine there was a speedy and progressive destruction of the islands of Langerhans. At the same time, marked destruction of the acini took place, so that our observations offer as much support for the acinar theory as for the island theory of the origin of diabetes. The view that alterations in the acini are the cause of diabetes is held by Hansemann,[2] Herxheimer,[3] Gutmann,[4] Schmidt,[5] and Karakascheff.[6]

III. Limit of Assimilation Increased by Feeding Fresh Pancreas. Pflüger[7] has shown in a careful critical study that the glycosuria in diabetes has never been diminished by the introduction into the body of pancreas or pancreatic preparations. Zuelzer[8] has recently claimed that he has caused a temporary decrease in the amount of sugar in the urine of diabetic men and dogs by the intravenous injection of a pancreatic "hormone." It seems quite evident from the studies of Forschbach[9] that the decreased elimination of sugar was due to the toxic action of the material injected rather than to the presence of a specific substance in the preparation.

[1] Archiv f. d. ges. Physiol, 1907, cxviii, 536.
[2] Verhdl. d. deut. pathol. Gesellsch. Berlin, 1901, iv, 187.
[3] Virchow's Archiv, 1906, clxxxiii, 228.
[4] Ibid., 1903, clxxii, 493.
[5] Münch. med. Wochenschr., 1902, p. 52.
[6] Deutsch. Arch. f. klin. Med., 1904, lxxxii, 60.
[7] Arch. f. d. ges. Physiol., 1907, cxviii, 267.
[8] Zeitschr. f. exp. Path. u. Ther., 1908, v, 307.
[9] Deutsch. med. Wochnschr., 1909, 2053.

Hédon[1] has asserted that the existence of the internal secretion of the pancreas will not be demonstrated until it is possible to check diabetes in a depancreatized dog by the introduction of a pancreatic product.

The study of the effect of feeding fresh pancreas to animals with lowered limit of assimilation for glucose was undertaken, with the hope of gaining some information in regard to the internal secretion of the pancreas. The limit of assimilation in Dog V was tested at frequent intervals over a period of fourteen months following the separation of the pancreas from the duodenum. As has already been stated, the tolerance for glucose varied during this time from less than 3.8 grams per kilo of body weight to more than 5 grams per kilo. On January 12, 1910, nearly fourteen months after the operation the feeding of 30 grams of glucose produced glycosuria. From February 3 to March 18 the dog was fed two to three raw pancreas a day. The limit of assimilation rose rapidly and steadily, as is shown in Table VIII. On March 17, the day the administration of pancreas was discontinued, limit of assimilation was more than 13.8 grams per kilo, which represented an increase of more than 100 per cent. in the dog's power to destroy glucose. While the pancreas was fed the absorption of fat and protein was almost normal, and the dog gained more than 2 kilos. As soon as the feeding of the gland was discontinued there was a loss of weight. The limit of assimilation did not fall for more than a month afterward. This is a remarkable fact. The test made on April 30, six weeks after the last fresh pancreas had been given, showed that this dog, with an atrophied and sclerotic pancreas, had a greater power to assimilate sugar per kilo of body weight than any normal animal in our series. It would be futile to speculate on the cause of this increase until more experimental data have been accumulated.

Summary. There is a rapid decrease in the power to assimilate glucose after the onset of atrophy of the pancreas.

The persistence of the low limit of assimilation for more than a year shows that the other organs of the body compensated imperfectly, if at all, for the pancreatic insufficiency.

[1] Travaux der Physiologie, 1898. Quoted by Pflüger.

Diabetes did not develop in any animal, although in two the atrophy and sclerosis of the pancreas were extreme. It cannot be denied that the retained ability to consume sugar in animals with the pancreas almost totally sclerosed was possibly due to some compensating action elsewhere in the organism.

The limit of assimilation in a dog with atrophy of the pancreas that had been under observation fourteen months was increased more than 100 per cent. by feeding fresh pancreas.

In two dogs there was complete disappearance of the islands of Langerhans in the atrophied pancreas without the occurrence of diabetes. This would indicate that the acini were able to perform the internal function of the pancreas.

DISCUSSION.

Dr. Henry Sewall: It may not be out of place at this time to refer to some observations I have carried out during the last two months on a case of youthful diabetes. The patient was a girl, aged eight years, in whom a slight glycosuria persisted on the strictest diet. Without going into detail, it may be said that interesting and encouraging results followed the administration by mouth of infusions of lean beef and of pancreas. When the patient excreted from 15 to 20 grains of sugar per diem this amount was several times annihilated by giving the infusions in a certain sequence. The method usually employed was to mince in a sausage grinder from 3 to 6 ounces of fresh beef's pancreas and extract it for some hours in a quart of cold water to which was added 1 dram of dilute HCl. The fluid was then strained off, and to it was added one pound of ground beef. The juice was again strained off after several hours and drunk by the patient in the course of a day. A slight reduction in the glycosuria occurred. But on the following day, when a similar infusion, made from the pancreas alone, was given, the sugar completely disappeared. For some days thereafter it was found that sugar could be abolished from the urine by a sequence of beef infusion and pancreatic infusion. But later it was necessary to return to the original maneuver. More extended experience has shown the method ineffective in many cases.

Dr. William G. MacCallum: In discussing a similar paper last year I mentioned an experiment which we had at the time under observation. In that experiment the anterior branch of the dog's pancreas was ligated off and allowed to remain for many months. At a second operation the obstructed portion was found to be represented by only a thin film of tissue; nevertheless,

the removal of the remainder of the pancreas was followed by only a transient glycosuria, after which the dog showed a considerable tolerance for carbohydrates. When the remaining film was removed a fatal glycosuria ensued. In this film were masses of cells which we regarded as islands of Langerhans, although these are at best vaguely outlined in the dog, and when embedded in scar tissue and brought close together are difficult to recognize.

Dr. A. E. Taylor: In the absence of a specific histological stain for the elements of the islands of Langerhans, it ought to be recognized that the ordinary histological methods are not competent in the crucial question at issue. There is an enormous mass of physiological and experimental literature bearing on the relations of the pancreas to diabetes and the sugar metabolism. To place this mass of research at the mercy, so to speak, of an unspecialized histological method, is dangerous precedent and practice. We are dealing with cellular remnants located in abnormal tissues and tissue relations. I have seen specimens bearing upon just this point regarding which competent histologists were in direct contradiction.

Dr. Joseph H. Pratt: I worked with cats as well as dogs. In cats the islands of Langerhans stand out in sharper contrast to the surrounding acini than they do in dogs. The changes in the pancreas which occur as a result of the separation of the pancreas from the duodenum have been studied in a series of animals dying at intervals varying from two weeks to five months after the operation. In this way the increasing alterations in the islands could be followed. The cells of the acini sometimes lose their blue-staining granules and then they resemble the cells of the islands of Langerhans. In atrophy of the pancreas due to occlusion of the ducts, the acini which no longer furnish the external secretion to the intestine may, for all we know, contribute something to the blood. In other words, the acini possibly take part in the internal secretion of the pancreas. If all the islands are destroyed and diabetes does not supervene, then the internal function of the pancreas must be performed by the acini.

The feeding of fresh pancreas or pancreatic preparations does not diminish the glycosuria in ordinary diabetes. It is possible that idiopathic diabetes in man is quite a different condition from diabetes due to gross lesions of the pancreas or to extirpation of the gland.

I have under observation a man who, in 1903, suffered from acute hemorrhagic pancreatitis. A large amount of necrotic pancreatic tissue was found at the operation. Three or four years ago diabetes developed. In this case the diabetes is clearly due to lack of pancreatic tissue. It furnishes an ideal opportunity to study the effect of feeding fresh pancreas in a case of pure pancreatic diabetes. I intend to try this form of treatment on my return home.

ORTHODIAGRAPHY IN PATHOLOGICAL CONDITIONS OF THE HEART AND AORTA.

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It is scarcely necessary to say that any instrument or method of examination which renders the science of medicine more exact, or which enables us to make more complete and accurate records of pathological findings, should be appreciated by the profession, even though the field of usefulness be comparatively small.

The orthodiagraph is an instrument which enables us to outline in its exact size any organ or object of which the Röntgen rays will cast a sufficient shadow. This result is obtained by carrying a small pencil of the rays through a series of parallel positions about the borders of the object under observation, and recording the results upon a sheet of paper placed behind the subject.[1] By fixing at the same time landmarks, such as the outline of the body, the ribs, the diaphragm, etc., the orientation of the object or organ may be made exact.

Accuracy of Results.—We speak of outlining the object under observation in its exact size, but such a statement requires some modification. The heart and aorta are in constant motion, expanding and contracting, and it therefore becomes necessary to choose which part of the cycle is to be pictured. We have chosen expansion because it allows of greater accuracy, it being easier to mark the

[1] For description of the technique, see American Journal of the Medical Sciences, October, 1909.—Claytor and Merrill.

shadow of the heart or aorta as it makes its widest excursion into the light area of the lungs. If the heart is pulsating very rapidly it becomes much more difficult to make a correct diagram, because of the fleeting character of the shadow cast. The condition of the lungs is also very important. If they contain dark areas in the neighborhood of the great vessels, it may be impossible to obtain satisfactory results. A marked œdema, due to cardiac weakness, may also render it impossible to outline the heart.

The Practical Value of Orthodiagraphy.—Last May[1] we presented to the Association of American Physicians a series of tables compiled from orthodiagrams of the hearts of about one hundred normal men and women, showing the measurements of the anterior projection of the heart's shadow for various weights (the division according to weight was found to be the most practical method). By reference to these tables it is possible to tell just how much and in what direction a heart shadow under consideration may depart from the average. However, after some experience in making diagrams of the heart, it is seldom necessary to resort to the actual measurement of the resulting figure, as one may see at a glance whether or not there is any material distortion of the outline. It should also be remembered that even in normal individuals of like height and weight there may be considerable difference in the size of the heart.

Possibilities of Error in Orthodiagraphy.—There is seldom any difficulty in fixing the landmarks, as they may be called. The outline of the neck, shoulders, and body, together with the position of as many of the ribs as are desired, can be marked with the pointer before the current is turned on. The interior of the thoracic cavity is easily marked if the lungs are clear, and the position of the diaphragm determined at any stage of the respiratory cycle which may be desired. We have found that the median line is more accurate when established by measurements made from the lateral aspects of the interior of the thoracic cavity, as the xiphoid is so often distorted and the umbilicus is a little too low for convenience as a fixed median point.

[1] Claytor and Merrill: American Journal of the Medical Sciences, October, 1909; Trans. Assoc. American Physicians, 1909, vol. xxiv.

The right auricular curve is usually clearly seen, but on reaching the right vascular curve there may be some difficulty. If this curve happens to be formed by a dilated ascending aorta, its pulsations render it easy of recognition, but if the descending cava is the object to be outlined the absence of motion makes it more difficult to distinguish, as enlarged or dark glands may be projected into this area. The aortic curve, while in some instances casting but a faint shadow, can usually be clearly seen. Below this the pulmonary curve, made by the pulmonary artery as it plunges beneath the arch of the aorta, comes into view. Then the left auricular curve may be seen. In normal cases this curve is often not perceptible, as it is produced by the left auricular appendix, while in instances of dilated left auricle, this portion of the heart casts the shadow. The left auricular curve is most marked in stenosis of the mitral valve. Below this comes the left ventricular curve, which is usually clearly seen until the apex is reached, when, because of its transparency, rapid and wide excursion of movement, and because of its close proximity to the diaphragm in all cases, and to the liver in some cases, it is more difficult to see.

There is sometimes difficulty in distinguishing a dilated aorta from a true aneurysm (Fig. No. 5), but in most instances aneurysms of the ascending, transverse, and descending aorta are clearly seen. The condition of the lungs in aneurysmal cases is sometimes such as to render it impossible to outline the dilated vessel except in its upper portion.

It has been pointed out by Franz M. Groedel[1] that it is very necessary to bear in mind the remarkable mobility of the heart. Thus, diagrams taken of the same object in the same position during quiet respiration, inflation, and deflation of the lungs, may show a marked difference in the cardiac outline. Fig. 4 illustrates this change. If this fact is lost sight of it is easy to draw false conclusions as to the efficacy of exercises and baths in causing surprisingly sudden and improbable alterations in the area of cardiac dulness. We have shown elsewhere the effect of change of bodily position upon the heart.[2] Furthermore, it should be remembered that the

[1] Zeitschrift für Balnologie, Klimatologie, und Kurort. Hygiene, II Jahrgang, 1909–1910, Berlin, SW. 48.

[2] Claytor and Merrill, loc. cit.

heart rests upon the diaphragm in close proximity to the stomach and the liver, so that distention of the former or enlargement of the latter may cause a deflection of this organ to the left or right, thus giving the impression of enlargement on the side toward which it is deflected.

Aneurysms of the Thoracic Aorta. In the study of aneurysms of the thoracic aorta the orthodiagraph is of real value. With it we are enabled to reproduce diagrammatically the dilated aorta in its exact size, and thus, while making or confirming a diagnosis of the pathological condition by a fluoroscopic examination, we are able to add materially to our historic record of the case. There would seem to be no doubt of the fact that a direct inspection of the heart and great vessels by means of the fluoroscope is of far greater value than an *x*-ray picture. By direct inspection we can detect the pulsations of the aneurysm and thus distinguish it, in most cases at least, from solid intrathoracic tumors; whereas, the radiographic picture would show only a shadow, which might be either aneurysm or some form of tumor or glandular enlargement. The oblique illumination is also useful in studying thoracic aneurysms.

Valvular Lesions. It has long been known that certain valvular lesions have a tendency to cause dilatation and hypertrophy of the various divisions of the heart, this having been proved not only by the anatomical findings after death, but by percussion of the cardiac region during life. In the orthodiagraph we have an excellent instrument for making interesting and more or less valuable records of these changes in the heart's outline. We alluded to this in our previous work, but only very briefly.[1] We have selected for illustration from our collection of diagrams of pathological conditions of the heart a few in which the lesions seemed to be sufficiently clear cut to be of value in this paper. Of course, when a number of valvular lesions co-exist, there can be nothing distinctive about the cardiogram. While there is no doubt that the different valvular lesions cause the heart to enlarge in a more or less characteristic manner, yet it must not be forgotten that this is not invariably the case. The heart that has been for any prolonged period in the state of lost compensation becomes more or less generally dilated, and thus

[1] Claytor and Merrill, loc. cit.

there is likely to be lost any characteristic outline which may at an earlier date have been present.

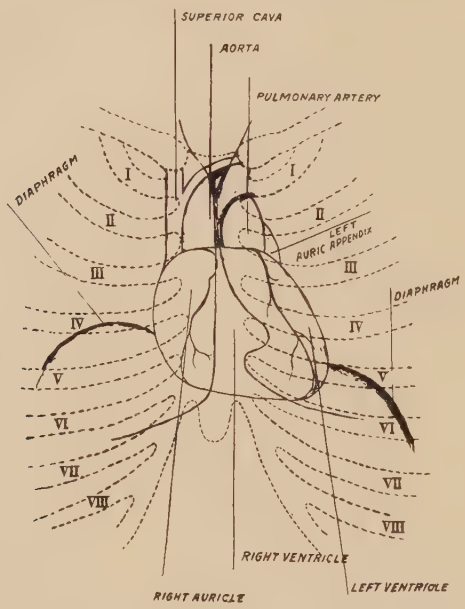

FIG. 1.—The normal heart and great vessels as seen from in front (after Moritz somewhat modified).

FIG. 2.—Illustration of the method of outlining the heart and landmarks (heart of aortic insufficiency).

DESCRIPTION OF ORTHODIAGRAMS. Fig. 1, a somewhat modified diagram after Moritz,[1] shows the normal heart and great vessels as seen from before.

[1] Strassburg. Med. Zeit., August, 1907.

Fig. 2 shows how the neck, shoulders, body, diaphragm, and heart are outlined by dots (the heart of aortic insufficiency).

Fig. 3 shows a completed diagram of a normal heart: (1) "right auricular curve;" (2) "curve of the great vessels;" (3) aortic curve; (4) pulmonary curve; (5) left auricular curve; (6) left ventricular curve; together with the lines upon which the size of the heart is estimated (L.D., longitudinal diameter; T.D., transverse diameter the sum of M.R. and M.L.).

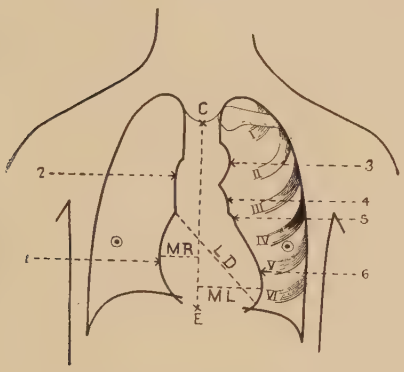

Fig. 3.—Orthodiagram of the normal heart.

Fig. 4.—Alterations in cardiac outline due to changes in the position of the diaphragm.

Fig. 4, a continuous line, shows the diagram of the heart and diaphragm during quiet respiration. The broken line shows the same during extreme expiration, while the diagram formed by the dots and dashes is taken during deep inspiration. This figure clearly indicates the remarkable mobility of the heart and, one might say, flexibility of its walls, thus accounting for many mistaken ideas as to the sudden changes in the actual size of the organ as demonstrated by percussion.

Fig. 5 is of the heart of a man, aged sixty-six years, who presented the typical signs of an aortic insufficiency. The chief point of interest was as to whether the very marked aortic curve was due to a true aneurysm or only to the dilatation of the arch of the aorta, so often seen in aortic insufficiency. Since our notice was called by Dr. F. H. Williams to the remarkably wide excursion of the aortic

pulsation in cases of insufficiency of the aortic valve we have frequently noted its occurrence.

Fig. 6 is from a patient with a very large aneurysm of the arch and descending limb of the aorta. Because of the congested and possibly infiltrated condition of the left lung, as the result of pressure, it was only possible to outline the upper portion of the enlargement.

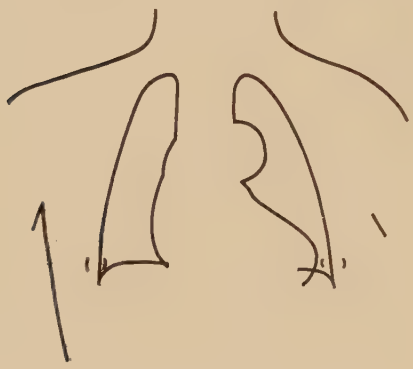

Fig. 5.—Aortic insufficiency—possibly also thoracic aneurysm.

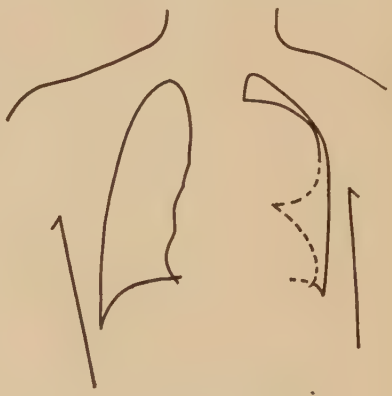

Fig. 6.—Aneurysm of the aorta.

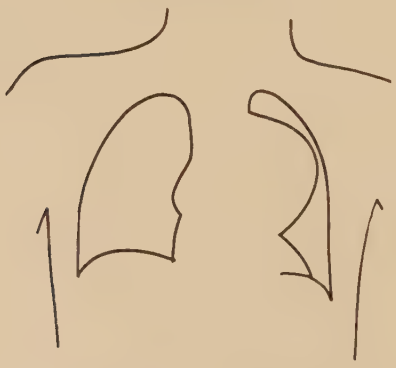

Fig. 7.—Diagram of a thoracic aneurysm.

Fig. 8.—The same case three months later.

The broken line indicates the probable position of the lower part of the dilatation and of the heart.

Figs. 7 and 8 are two diagrams of the same aneurysm, the second having been taken about three months after the first. There has been practically no change, the apparent difference in the size of the heart

being due to the fact that the left side of the diaphragm was taken in a lower position in one figure than in the other.

Figs. 9 and 10 are two of our most instructive diagrams, Fig. 9 having been taken sixteen months later than Fig. 10. It may be clearly seen that the aneurysm which is depicted has markedly increased both to the right and to the left. The heart has also enlarged. The prognostic value of the orthodiagraph is here demonstrated. (This patient was seen through the courtesy of Dr. R. W. Baker.)

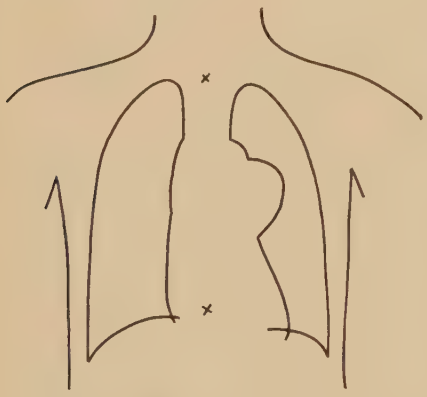

Fig. 9.—Diagram of a thoracic aneurysm.

Fig. 10.—The same case sixteen months later.

In a study of changes produced in the heart's silhouette by the various valvular lesions, there are several things to be considered: namely, the age of the patient—the heart in the aged shows a tendency to enlarge and to assume a more oblique position in the chest; the presence of other causes for cardiac hypertrophy, such as arteriosclerosis, chronic nephritis, etc.; the appearance may also vary, depending upon whether the valvular lesion be single or double, or multiple, or whether there has ever been any actual loss of compensation. All of these points, and others not enumerated, are of considerable importance in drawing conclusions concerning a diagram.

Fig. 11 is a diagram of the heart of a man, aged thirty-six years, presenting the physical signs of a mitral insufficiency with good compensation. The organ is in the vertical position. The pulmonary and

left auricular curves, while indistinguishable in this instance, are enlarged, making the cardiogram rise toward the left axilla. The left ventricular curve is only moderately increased.

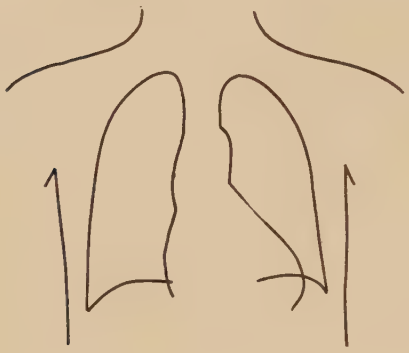

Fig. 11.—Mitral insufficiency.

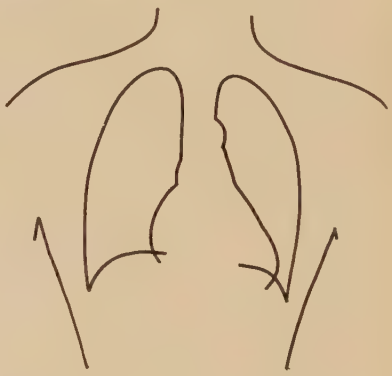

Fig. 12.—Mitral stenosis, well compensated.

Fig. 12 shows the outline of a case of compensated mitral stenosis in a woman, aged thirty-seven years. The chief characteristics are the decidedly vertical position in the chest, the rather full right

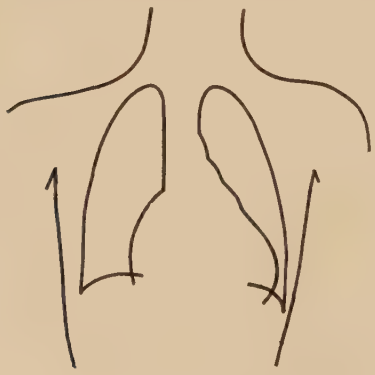

Fig. 13.—Mitral stenosis after prolonged loss of compensation.

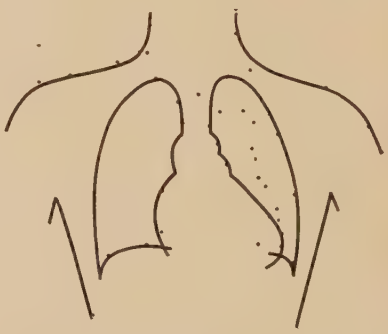

Fig. 14.—Mitral insufficiency and stenosis.

auricular and pulmonary curves, but most striking of all the increase in size of the left auricular curve with the relatively small left ventricular curve, which is just what would be expected, because of the fact that there is seldom much increase in the size of the left ventricle in pure mitral stenosis.

Fig. 13 shows the heart of a young woman, aged twenty-five years, with a pure mitral stenosis, which, however, has passed through a long period of broken compensation. The whole heart is greatly enlarged. The striking features are the bulging right auricular, pulmonary, and left auricular curves. The outline of the heart with a double lesion may vary, we believe, with the priority of the affection. Thus, in the case of the mitral valve, if the insufficiency be the primary trouble, the left ventricular curve will be much more pronounced than when the stenosis has been primary.

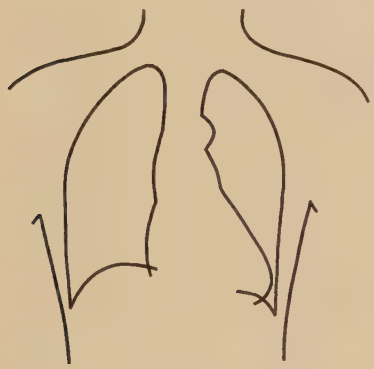

Fig. 15.—Double mitral lesion.

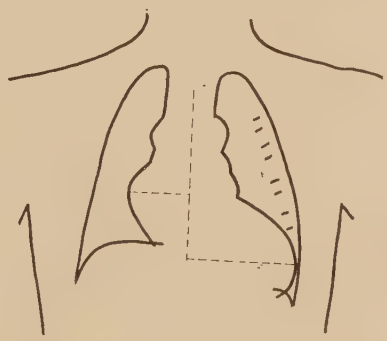

Fig. 16.—Mitral and aortic insufficiency.

Fig. 14 is of a heart presenting a double mitral lesion in which the stenosis is probably the more important; while in Fig. 15 the insufficiency was probably the prior lesion. In both, the right vascular, pulmonary, and left auricular curves are bulging, but in Fig. 15 the left ventricle shows greater hypertrophy. In Fig. 2 we have an excellent example of a pure aortic insufficiency in a man aged thirty-five years. Both the longitudinal and transverse diameters are considerably increased. The heart is obliquely situated, and is foot-shaped. With this lesion the right vascular and aortic curves are especially marked because of the dilated condition of the aorta which is so commonly observed. In aortic stenosis the shape of the heart is said to be much the same, but there is no dilatation of the aorta.

Fig. 16 is an example of a combined aortic and mitral insufficiency in a man aged fifty years. In this instance the aortic was the

primary lesion, having preceded the mitral by several years. The hypertrophy and dilatation were enormous, all the curves being greatly exaggerated.

In Fig. 17 are presented the same lesions in a woman aged forty years. From the shape of this heart the mitral lesion probably antedated, or was more important, than the aortic.

Fig. 17.—Mitral and aortic insufficiency, the mitral probably the more important.

Fig. 18.—Double aortic lesion.

Fig. 18 is from a man, aged sixty-six years, with a double aortic murmur. Upon the right side of the heart it may be seen that the right auricular and right vascular curve form a continuous and almost straight line, and this we believe is due to the fact that the pericardium is outlined, instead of the heart itself.

Fig. 19 is from a young woman who has given evidences from childhood of a moderate degree of cardiac insufficiency. There is a harsh systolic murmur heard over the entire præcordia, with greatest intensity in the second and third interspaces to the left of the sternum. The heart is rather uniformly enlarged, but the point of interest is the great size of the pulmonary curve, which, as may be seen, is relatively much larger than the aortic. The diagnosis of congenital hypoplasia of the aorta was made some years ago by a very careful observer, and this diagram would appear to support this diagnosis.

Fig. 20 is from a man, aged forty-five years, five feet six and one-half inches in height, and weighing 175 pounds. There was a general

arteriofibrosis, with high systolic blood pressure, but a perfectly normal urine. There were no endocardial murmurs, and the heart would appear to be uniformly enlarged.

FIG. 19.—Congenital hypoplasia of the aorta.

FIG. 20.—From a case of general arteriosclerosis.

It seems unnecessary to multiply diagrams. From those shown it may be seen that the orthodiagraph is of real value to the clinician, and that as it becomes more commonly used we may be able to formulate some useful facts which as yet it is unwise to attempt. The instrument is by no means necessary in all cases, but may be a useful aid in many more or less obscure pathological conditions of the heart and aorta.

PERSONAL EXPERIENCE IN ELECTROCARDIOGRAPHIC WORK WITH THE USE OF THE EDELMANN STRING GALVANOMETER (SMALLER MODEL).

By LEWELLYS F. BARKER, M.D., A. D. HIRSCHFELDER, M.D.,
AND
GEORGE M. BOND, M.D.

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During the last year the writers have been engaged in testing the value of the string galvanometer of Edelmann (smaller model) in clinical work. After the preliminary difficulties of technique were overcome fairly satisfactory tracings were obtained, as the curves accompanying the cases here published will show.

The principles of electrocardiography and a general review of the results thus far obtained by other workers are discussed at length in another paper written by one of us.[1] Our own work has convinced us that electrocardiography and electrophonography are valuable clinical methods of investigation as supplements to the ordinary methods of physical diagnosis. While it is desirable, where possible, to make use of two galvanometers, one large one for electrocardiograms and a small one for the simultaneous registration of electrophonograms, much can be accomplished with the small apparatus alone. Where both the larger and the smaller apparatus can be installed, it is advisable to have them, but if for any reason only the smaller instrument is available valuable results can be obtained with it alone.

[1] L. F. Barker, Electrocardiography and Electrophonography, Johns Hopkins Hospital Bulletin, December, 1910.

Physicians working with the instruments must have patience to overcome the preliminary technical difficulties; once these have been mastered electrocardiograms can be taken with very little expenditure of time and trouble. The procedure has now passed the experimental stage and will doubtless form a part of the instrumental armamentarium of the larger general hospitals.

Tests of the Delicacy of the String Galvanometer.

After a few tracings were made with a rather loose string, it was found that the best results were obtained when the latter was rather taut, *i. e.*, with the index upon the scale pointing to 10. The excursions given by known currents are shown on the tracings: 0.001 volt gives an excursion of 3 mm.; 0.0002 volt gives an excursion of less than 1 mm. (Fig. 1).

There is practically no lag, the curve being nearly vertical. At the breaking of the current the string returns to its former level with equal promptness. A typical electrocardiogram is shown in Fig. 2.

Transient Atrial Paralysis during an Attack of Heart Failure in a Patient with Chronic Myocardial Disease. Resumption of Function by the Atrium after Subsidence of the Heart Failure.

J. J. W., white, male, aged sixty-seven years, was admitted to the hospital January 20, 1910, complaining of "heart trouble."

When six years old the patient had measles and whooping cough. Except for some bronchitis in winter, patient was unusually very healthy and never had tonsilitis. He gives the history of both lues and gonorrhœa seven years ago. He uses alcohol to excess and is greatly exposed to the weather.

His present illness began in December, 1909, with a "weak feeling over the heart and shortness of breath on exertion." He also had a bad cough with pain in the chest on coughing and it was accompanied by headache and night sweats. Five days before admission he awoke during the night with a "rapid fluttering heart" and a

"stinging pain in the heart region." These symptoms remained until his admission into the hospital, together with some fever and sweating, but no chills.

On examination his lips, face, and ears were cyanotic. There was marked pyorrhœa alveolaris. The tonsils were not enlarged. There was marked precordial bulging and a heaving cardiac impulse at the apex. There was marked irregularity in force and rhythm. The heart was enlarged. The area of cardiac dulness extended 13 cm. to the left and 5 cm. to the right of the midsternal line. No thrills could be felt. The sounds were irregular in intensity and rhythm and somewhat distant, but no murmurs were heard. There was a presystolic gallop and an occasional extrasystole.

The liver was enlarged, presented a smooth surface, and palpation revealed marked tenderness. There was no ascites or edema.

The pulse was small, soft, and irregular, 68 per minute, while the heart rate was 100 per minute.

The electrocardiogram (Fig. 3) taken at this period shows only a large first ventricular (R) wave. The wave (P) due to the atrial contraction and the second ventricular wave (T) are absent, *i. e.*, there is atrial paralysis and ventricular weakness. Phlebographic tracings made from the right jugular vein also showed atrial paralysis. Both electrocardiograms and phlebograms show the presence of an absolute arrhythmia. No definite extrasystoles were made out.

Two weeks later, however, when the decompensation had passed off and the pulse rate was regular, the electrocardiogram had also become normal, and the atrial (P) wave had reappeared.

Mitral Insufficiency; Hypertrophy of the Left Ventricle; Cardiac Arrhythmia.

P. M., white, male, aged thirty-four years, entered the hospital February 4, 1910, complaining of "pain in back and left side, weakness, and shortness of breath."

He had always been in good health except for measles as a child and malaria ten years ago. He denies lues or gonorrhœal infection, but admits using tobacco and alcohol very freely. He has never been troubled with cardiorespiratory symptoms before.

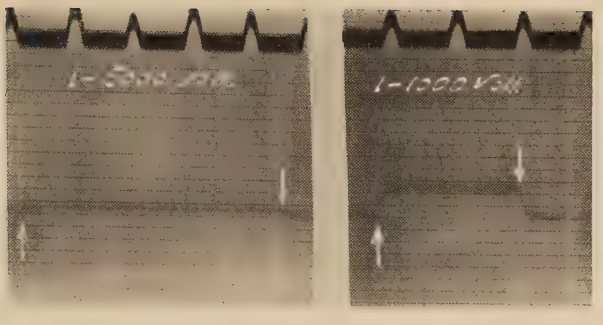

Fig. 1.—Excursions due to currents of known strength.

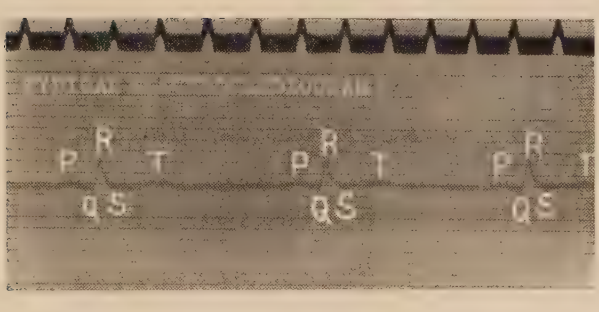

Fig. 2.—Typical electrocardiogram when curve is made with small model.

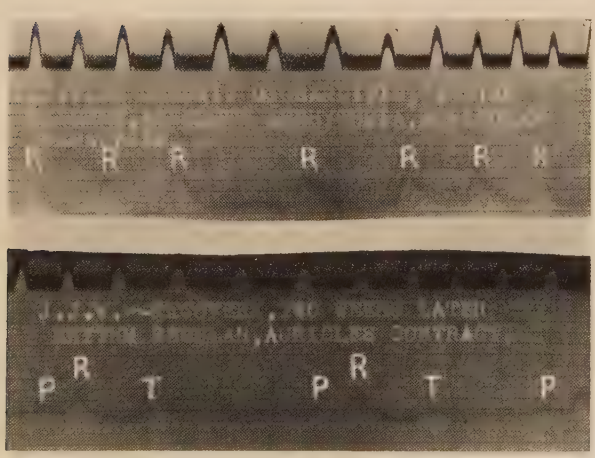

Fig. 3.—Electrocardiograms before and after treatment of the patient J. J. W.

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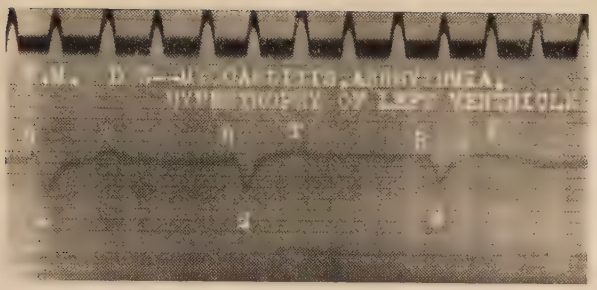

Fig. 4.—Electrocardiogram from the patient P. M. Hypertrophy of left ventricle.

Fig. 5.—Phlebogram and electrocardiogram from the patient W. P., illustrating the occurrence of the "left ventricular" types of extrasystoles.

Fig. 6.—Electrocardiograms from the patient W. P. The upper curve was taken in an interval between attacks of paroxysmal tachycardia. The curve has a fairly typical form except that the P wave is relatively exaggerated, owing to the atrial hypertrophy due to the mitral stenosis. In the lower curve the interval between two R waves suggests transitory atrial fibrillation.

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His present illness began in July, 1909, when he fell unconscious, and afterward his left foot dragged. The next day he felt faint and cold, but did not lose consciousness. Every attempt at eating caused vomiting, for, as he put it, "It seemed to cut off his breath until vomiting took place." Since this attack he has felt giddy and his heart beat very rapidly when he tried to walk. Two weeks ago he began to have pain in the back, with fever and headache.

The examination at the time that the electrocardiograms were taken showed cyanosis of the face, lips, and ears, with short, rapid respirations. The tonsils were not enlarged, but there was very marked pyorrhœa alveolaris. There was marked glandular enlargement. The lungs were clear throughout. The heart was slightly enlarged and the sounds were everywhere clear. There was a faint systolic murmur at the apex which was transmitted to the axilla. The pulse was irregular, 80 to the minute, of fair volume and low tension. The liver was slightly enlarged, but was not tender.

The Wassermann reaction was negative. Examination of the urine revealed nothing abnormal. The maximal blood pressure varied from 100 to 120, and the temperature and pulse were practically normal. The respirations were slightly quickened.

The electrocardiogram (D 3) shows inversion of the typical curve (Fig. 4). There is a small R wave followed by a very well-marked S depression which is the most striking feature of the tracing and is characteristic of hypertrophy of the left ventricle. In contrast to the tracing of C. L. the T wave in this curve is normal. The atrial wave (P) is absent, for the atria do not contract.

Left Ventricular Extrasystoles and Atrial Fibrillation in a Patient with Mitral Stenosis and Insufficiency, Aortic Insufficiency (?), Paroxysmal Tachycardia, and Arthritis of the Cervical Vertebræ.

William P., white, aged twenty-eight years, entered the hospital January 7, 1910, complaining of "attacks of tachycardia, weakness, and dizziness." There is nothing of importance in his family history. As a child he had measles, mumps, whooping cough, and

scarlet fever, but has never had tonsillitis. At the age of sixteen he suffered from a severe attack of "rheumatism" which affected both knees and lasted for a week and a half.

He has been admitted to this hospital on five previous occasions, the first being March 20, 1907, when he showed enlarged tonsils, some soreness in the joints, mitral stenosis and insufficiency, with aortic insufficiency.

On April 26, 1907, the tonsils were removed, and he later developed a subacute otitis media. On his third admission, January 29, 1909, he complained of attacks of tachycardia, which began and ended abruptly. At this time on examination tenderness in the cervical spine was noted. In his last two admissions, April 5, 1909, and April 12, 1909, these attacks were becoming more frequent. His last admission showed an absence of the aortic diastolic murmur.

Between this and the present admission the attacks of tachycardia have become more frequent, and their duration has varied from thirty seconds to eight and one-half hours. The onset and cessation are very sudden, while the pulse rate before and during an attack changes from 70 to 80 to 170 to 190. The attacks usually end spontaneously, and it has not been possible to stop them by mechanical means nor by drugs—not even by intravenous strophanthin. The attacks are usually accompanied by weakness, dyspnœa, and a sense of oppression.

On examination the following facts were brought out: There was no cyanosis; the mouth was clear. The neck showed a slightly enlarged thyroid and some glandular enlargement. The heart was slightly enlarged, the impulse was diffuse, and there was a presystolic thrill ending in a tapping shock coincident with the first sound. Audible at the apex was a long rough presystolic murmur ending in a snapping first sound. This was followed by a soft systolic murmur which was transmitted into the axilla. In the aortic region there was a soft systolic murmur and a faint diastolic blow, heard best at the left border of the sternum. The aortic second was muffled and reduplicated. The pulmonic second was much accentuated. There was slight retrosternal dulness. The liver and spleen were not enlarged.

At the beginning of an attack the pulse suddenly increased to 184.

The rhythm was regular; there were no extrasystoles; the beats were well sustained and the murmurs could all be made out. The patient was flushed and hot. The rate suddenly dropped to 72 with an apparent slight pause in the contractions. During his stay in the hospital these attacks averaged about four per week.

The urine was negative. The temperature was normal, and the maximal blood pressure varied from 100 to 120.

On February 22 when the second electrocardiogram was taken, the patient was complaining of some irregularity in the heart's action.

The phlebogram (Fig. 5) shows the presence of ventricular extrasystoles (E). In the electrocardiogram (D 2) these beats assume the form characteristic of extrasystoles arising in the left ventricle. The curves of the extrasystoles present an immense depression followed by an abnormally large and slow elevation.

On the same day the electrocardiogram (Fig. 6) also showed another form of irregularity. The P wave due to atrial contraction becomes irregular in size and position and is replaced by a series of irregular waves which are in some places superposed upon the R and T waves and in others superposed upon one another to form a sort of irregular plateau. These correspond to what Lewis in London, Winterberg and Rothberger in Vienna, have found to be due to atrial fibrillation in both man and animals, and support the atrial fibrillation theory of paroxysmal tachycardia.

Ventricular Extrasystoles of the Right Ventricular Type in a Patient with Mitral Stenosis.

Benjamin M., white, aged nine years, was admitted to the hospital complaining of "heart trouble." His family history was negative. The patient had mumps and whooping cough early in life and typhoid at the age of seven. Following a fright two years ago he has been very nervous, and one year ago was subject to convulsions with loss of consciousness. He has had both tonsils and adenoids removed. He came to the hospital on the present admission for other causes than the heart.

On examination he showed a slight cyanosis and some glandular enlargement with evident nasal obstruction. The thyroid was not enlarged. The heart extends 9 cm. to the left and 2½ cm. to the right of the midsternal line. The sounds are irregular in force and rhythm, with a presystolic gallop at times. The first sound is muffled, but no murmurs are heard, while the second is very sharp and of a snapping explosive character. The sounds are all clear at the base of the heart.

The pulse is small, quick, irregular, and of low tension. At times the extrasystoles give it a bigeminal character.

The urine is negative, and the maximal blood pressure varies from 90 to 100 mm. of mercury.

The electrocardiogram (D 2) shows (see Fig. 7) occasional extrasystoles which are the exact opposite of those shown by patient W. P. These abnormal waves are characterized by absence of the atrial wave P, by the presence of a very large positive wave which is followed by a very much exaggerated depression. This is the type which Kraus and Nicolai designate as extrasystoles arising in the right ventricle, though Kahn's studies have shown that this interpretation is by no means infallible.

Permanent Absolute Arrhythmia in a Patient with Myocardial Disease.

A. H., male, white, aged forty years, was admitted to the hospital September 27, 1909, with the complaint "shortness of breath and pain in the abdomen."

The patient has never had very many illnesses and no "rheumatism," tonsillitis, or cardiorespiratory disturbances. He had typhoid fever in 1905, and in 1908 "blood poisoning" accompanied by swelling of the glands in the left arm and axilla. He has used alcohol very little, but is a heavy smoker.

In the last year he has been very weak, with general lassitude and inability to work. Four days before admission he became very dyspnœic, with some orthopnœa and slight cough. He also noticed pain in the abdomen over the liver region

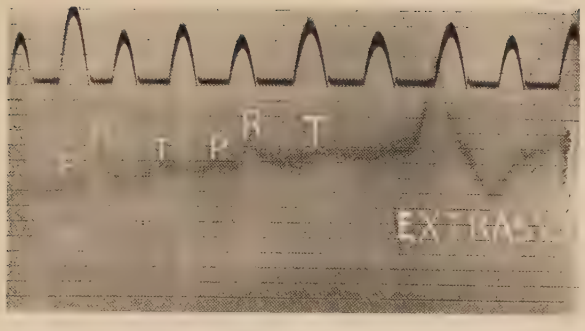

FIG. 7.—Electrocardiogram from the patient Benjamin M., illustrating the "right ventricular" type of extrasystolic irregularity.

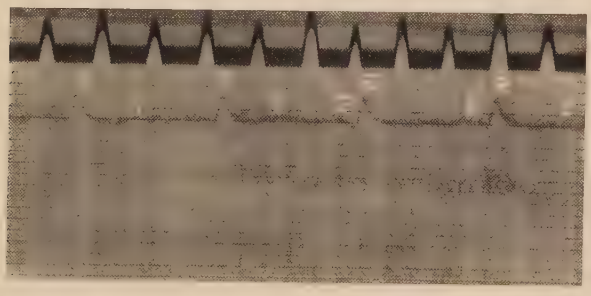

FIG. 8.—Electrocardiogram from the patient A. H. See text.

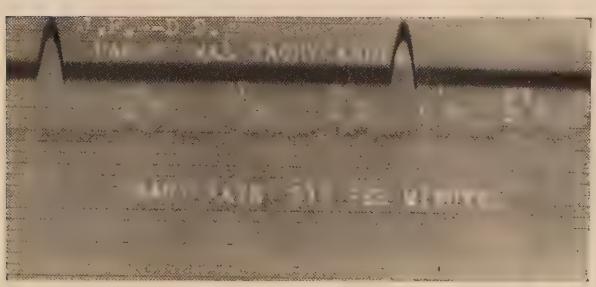

FIG. 9.—Electrogram from the patient J. F., illustrating one type of paroxysmal tachycardia.

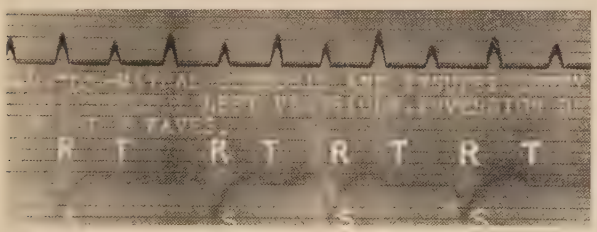

FIG. 10.—Electrocardiogram from the patient C. L. Hypertrophy of the left ventricle. Derivation III.

On examination the patient showed a dusky pallor with a slight icteric tint and marked cyanosis of the lips and hands. The tonsils were not enlarged. Moist rales were heard at the bases of the lungs. The heart was enlarged to the left 16 cm. from the midsternal line. There was no thrill or shock. The sounds were muffled, and at the apex there was a loud systolic murmur transmitted to the axilla. No other murmurs were made out. The pulmonic second was accentuated and reduplicated. The pulse was small, regular, 120 to the minute, and of low tension.

The liver was enlarged and tender, and the spleen was also enlarged. There was some ascites but no œdema. A small amount of bloody fluid was removed from the pericardial cavity. Maximal blood pressure was 100 mm. of mercury.

When the patient entered the hospital he was put on strict cardiac diet with digitalis and strophanthus. He seemed to improve for a time, but the symptoms suddenly returned more marked than before. Œdema of the extremities developed, soon followed by ascites and right-sided hydrothorax. He was then placed upon a milk diet, 48 ounces per day with nutrose added, and at the same time given daily intramuscular injections of strophanthin. Improvement began promptly and continued steadily until the patient was discharged from the hospital in March. He is now able to continue his work as an artist.[1]

The electrocardiogram (D 2), taken shortly before the patient's discharge from the hospital, is of almost normal appearance (Fig. 8), though the atrial (P) and the second systolic wave (T) are not very well marked. The arrhythmia, though less marked and not well shown upon this tracing, persisted. There were no definite extrasystoles. The tracing in D 3 showed inversion of the first ventricular wave indicative of hypertrophy of the left ventricle.

Paroxysmal Tachycardia without Atrial Fibrillation.
(*Tracing During the Attack.*)

J. F., male, white, aged fifty-seven years, was admitted to the hospital February 19, 1910, complaining of "pains in the limbs and back with attacks of tachycardia."

[1] In the summer of 1910 this patient developed an acute diabetes and died in an attack of air-hunger and diabetic coma.

His family history is negative and his health has always been fairly good. He had measles, mumps, whooping cough, and scarlet fever as a child, and since the age of thirty-seven has had "rheumatism." Attacks of rapid heart which come and go suddenly without apparent cause have troubled him his entire life. The heart beats very forcibly at these times and the patient feels weak and nauseated. He has never had any precordial pain. In the past six years he has had attacks of dyspnœa, which come on once or twice a week and last about ten minutes.

Five weeks ago his "rheumatism" became worse and his attack of tachycardia and dyspnœa have become more frequent.

On examination he showed marked emphysema, with a heart only slightly enlarged. The sounds were distant but clear, with a much accentuated pulmonary second. The pulse was regular, slow, of low volume and fair tension. The artery wall was moderately thickened.

The attack of tachycardia during which the electrocardiograms were taken was brought on by a change in position. It began very suddenly and lasted six hours, during which time the patient felt weak and drowsy. There was marked pulsation of the veins of the neck, but no dyspnœa or enlargement of the heart. The first sound was heard very distinctly, but the second sound was very indistinct. The attack stopped very suddenly, the rate falling from 47 to the quarter to 22 to the quarter.

The urine examination was negative, and the patient's pulse and temperature were normal. During his stay in the hospital the maximal blood pressure varied from 110 to 120 mm. of mercury.

Electrocardiogram (D 2) showed a pulse rate of 216 per minute with normal, though rather small and sluggish R and T waves of ventricular origin (Fig. 9). There was no sign of irregular waves ascribable to atrial fibrillation, and it is very probable that the atria were beating regularly, but that the waves (P) due to their impulses were fused with the telesystolic (T) waves of the preceding ventricular systole.

Hypertrophy of the Left Ventricle and Absolute Arrhythmia in a Patient with Mitral Stenosis and Insufficiency.

C. L., female, white, aged thirty-one years, entered the hospital December 6, 1909, complaining of "heart trouble, cough, and pain in stomach."

She never had tonsillitis or quinsy, but on October 31, 1909, in this hospital developed acute tonsillitis of short duration, which was accompanied by myocardial lesions. In the last four years she has been troubled with cough, dyspnœa, and fainting attacks upon exertion. One month ago her cough increased, with expectoration, together with dyspnœa and orthopnœa. A week ago she noticed a pain in the lower left quadrant of the abdomen, which was increased upon coughing or swallowing. There has been some swelling of feet and ankles.

On examination the face was puffy and cyanotic. The veins of the neck were distended. The pulse was irregular, of small volume and low tension, while many of the beats could scarcely be felt. The heart was enlarged 16 cm. to left and 4 cm. to right of mid-sternal line. The cardiohepatic angle was a right angle. At the apex the first sound was snapping, followed by a rough systolic murmur and preceded by a short echoing rumble. The second sound was feeble but clear. Over the sternum the systolic murmur becomes more blowing in character. The pulmonic second is much accentuated, while the aortic second is feeble but clear. No thrill could be made out. There is an occasional extrasystole. There is some enlargement of the liver and definite ascites.

The urine showed a trace of albumin and a few casts. The sputum contained red blood corpuscles and heart-failure cells.

The maximal blood pressure varied from 100 to 120 mm. of mercury.

The electrocardiogram (D 3) shows an inversion of the first ventricular wave (Fig. 10). The R wave above the line is very small, while the S (ventricular systolic) depression below it is very marked. The telesystolic wave (T) is inverted, and exists as a depression and not a crest. The atrial (P) wave is usually absent, but there is a

suggestion of such a wave preceding the third ventricular systole (R wave) shown upon the tracing. There was an absolute arrhythmia, and no extrasystoles were present in the tracings taken.

Complete Heart Block without Syncopal Attacks.

S. E. L., white, male, aged sixty-four years, entered the hospital March 15, 1910, complaining of "shortness of breath on exertion."

The family history is unimportant, and his previous history shows him to have been a very healthy active man whose only illnesses were quinsy in 1864 and 1866, followed by "rheumatism" in the thighs for two months in 1866. The joints were not affected. He has never used alcohol or tobacco.

His wife states that about 1875 she noticed that his pulse rate was about half as great as her own. He did not suffer with any cardiac disturbances, however, until January, 1910, when he began to notice shortness of breath on exertion, such as climbing stairs, etc. This symptom has not become any more severe, and there has been no fainting, vertigo, or any other symptoms referable to the heart.

On examination the heart was not enlarged. The impulse was feeble and no thrill was felt. The sounds were feeble and distant, while the rate was very slow, with an occasional extrasystole. Over both the apex and the right ventricle faint sounds were heard during the long pauses between the stronger contractions. There was sometimes one and there were sometimes two such sounds in each long pause. The liver and spleen were slightly enlarged and there was some pitting over the shins.

The *x*-rays showed a very sluggish contraction of the left ventricle as compared to normal, while the right atrium was enlarged and pulsating about twice as frequently as the ventricle.

The Wassermann reaction was negative. The urine was clear. The blood pressure was maximal at 110. Temperature and respirations were normal, and the pulse varied from 28 to 36.

The phlebogram (Fig. 11) from the right jugular vein shows a complete block with atrial (*a*) waves almost double the rate of the ventricular (*c*) waves, but bearing no definite relation to the latter.

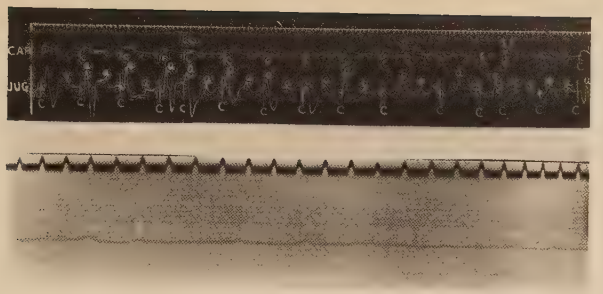

Fig. 11.—Tracings from a case of heart-block. Phlebogram above; electrocardiogram below.

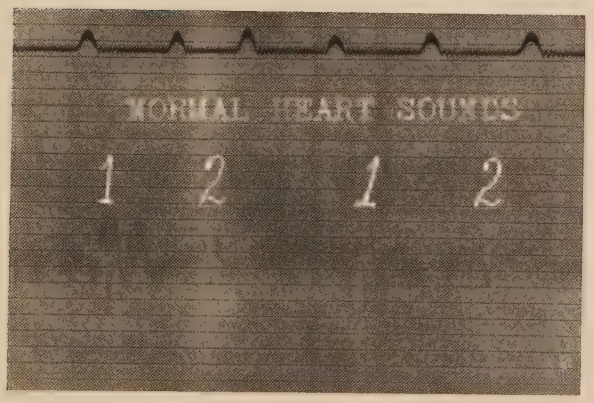

Fig. 12.—Cardiophenogram of normal heart sounds.

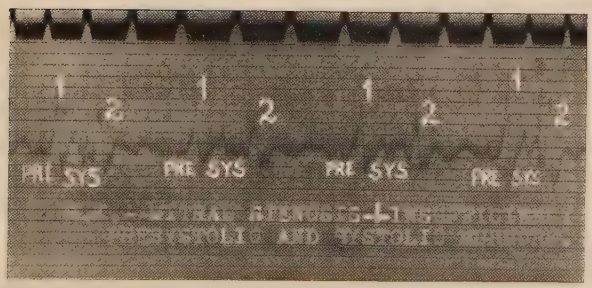

Fig. 13.—Cardiophenogram from the patient H. K., illustrating presystolic and systolic murmurs.

There are also occasional extrasystoles (E) of the ventricles, but the atrial rhythm is unaffected by them.

The electrocardiogram (D 2) shows the same complete block, which is, however, much more easily deciphered than on the phlebogram. The P waves, due to atrial impulses, bear no definite relation to the ventricular impulses (R and T waves).

The electrocardiograms in D 1 and D 3 show similar relations of atrium and ventricle.

Graphic Records of the Heart Sounds (Cardiophonograms).

The heart sounds were recorded in the manner described by Einthoven, Flohil, and Battaerd, by photographing the oscillations of the string galvanometer under the influence of the currents from a microphone. In other words, the string galvanometer is substituted in place of the receiver of a telephone and its movements are photographed. The sounds were conducted to the microphone from a small funnel or stethoscope bell placed over the patient's chest and thence through a rubber tube to the microphone. The greatest difficulty which we experienced, in common with all other observers upon this subject, consisted in doing away with the effects of jarring. Einthoven and his collaborators had succeeded by suspending their microphone upon a rather complicated Julius suspension apparatus, but we have been able to obtain quite satisfactory results by a much more simple device. The microphone itself was fitted upon a brass plate about ten inches square, which is suspended from the ceiling by three very light wires and is steadied by suspending two heavy window weights from its under surface. The microphone itself does not rest upon the plate itself, but is separated from it by a ring of rubber tubing. In order to do away with all jars to the microphone from handling the stethoscope, the tube from the latter leads first to a T tube which is fixed firmly upon a bracket in the wall. One arm of the T has an opening adjusted by a screw clamp, the other is connected with the microphone by a long, very thin-walled three-eighths inch rubber tube. It is important that this tube should be as soft and as flexible as possible.

When these precautions are taken, most, if not all, extraneous vibrations can be ruled out and satisfactory curves of the heart sounds can be obtained.

The first cardiophonogram (Fig. 12) shows record of the normal heart sound. The vibrations due to the first sound last from 0.10 to 0.14 second; the short pause lasts from 0.14 to 0.15 second. The vibrations due to the second sound last 0.06 second.

Cardiophonogram; Mitral Stenosis and Insufficiency.

H. K., white, aged eight years, came to the dispensary March 15, 1910, complaining of "rheumatism" and "heart trouble."

Her family history is unimportant, and she has always been a healthy child, with the exception of measles and whooping cough.

Her present trouble began four months ago with pain in the joints and loss of appetite. She was feverish at night, and suffered from dyspnœa on exertion.

On examination the heart was enlarged to the left 10 cm. from the midsternal line. A loud systolic murmur and presystolic rumble were heard.

The pulse was regular in force and rhythm with a frequency of 100 to the minute.

The electrocardiogram was of normal appearance.

The cardiophonogram from the apex (Fig. 13) shows large vibrations corresponding to the snapping first sound, which are preceded by small ones due to the presystolic rumble and followed by other small vibrations due to the systolic murmur. These terminate in the larger vibrations due to the second sound. During diastole there are a few vibrations corresponding to diastolic rumbles. The vibrations are quite similar in successive cardiac cycles.

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